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HEPATIC PATHOLOGY IN EXOPHTHALMIC GOITER*

By CARL VERNON WELLER, M.S., M.D., F.A.C.P., *Ann Arbor, Michigan*

IN A PRELIMINARY report¹ the writer has called attention to the frequent occurrence of chronic parenchymatous hepatitis in varying degrees in patients with Graves' disease. In the present paper the various lines of evidence bearing upon the coincidence of these conditions will be reviewed more completely, a somewhat more rigidly controlled series will be analyzed, and the lesions more fully described, than was possible in the earlier report.

There are four distinct avenues of approach to the problem of the nature of the interrelation between the liver and the thyroid gland, particularly as it concerns the hyperthyroid state. The gross and microscopic changes, with which the present investigation is primarily concerned, complement certain clinical, functional, and experimental observations which must first be reviewed.

I. ICTERUS IN EXOPHTHALMIC GOITER

The occurrence of icterus in patients presenting otherwise the signs and symptoms of exophthalmic goiter has been noted with sufficient frequency to justify investigation of this point. It must be recognized, as Lichtman² has recently emphasized, that in such cases the icterus may be an unrelated condition, and as such may be due to cholelithiasis, catarrhal jaundice, cholangitis, syphilis, or to any other of the various recognized causes. Also, icterus in exophthalmic goiter may be due to circulatory changes in the liver, associated with cardiac decompensation, thus bringing the liver condition into a somewhat remote relationship to the thyroid but without implying any specific etiological connection between the two. The frequency with which icterus is mentioned in case reports of exophthalmic goiter suggests that these two groups alone are inadequate to explain all examples and that a toxic action on liver tissue may be present.

Habershon³ (1874) noted the occurrence of jaundice in a patient with exophthalmic goiter, appearing 10 days before death and increasing markedly. As if to rule out the possibility that it might be due to chronic passive

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From the Department of Pathology, University of Michigan, Ann Arbor, Michigan.

congestion, he stated that the liver "was of a bright-yellow color, anemic, and in no way nutmegged." Eger,⁴ in 1880, observed icterus of the skin and conjunctiva in morbus Basedowii. The liver of this patient had a saffron-yellow parenchyma, perhaps largely because of lipoidosis, when it was seen at autopsy. Sutcliff⁵ (1898) found slight jaundice present in "an extraordinarily acute case of Graves' disease." Three cases of jaundice occurring in persons suffering from exophthalmic goiter were described by Eder⁶ in 1906. The third case can be discredited, since there was a history of cholelithiasis, but in the first there was no cardiac enlargement, and in the second the jaundice improved, although certain cardiac symptoms which were present remained unchanged. An extensive survey of the reported occurrence of icterus in exophthalmic goiter prior to 1908 is given by Sattler.⁷

Such observations as these have occurred sufficiently frequently to justify certain clinical generalizations which can be found among the more complete descriptions of exophthalmic goiter. Thus Boothby⁸ wrote of the "tendency to gastrointestinal crises of nausea, vomiting and diarrhea, with jaundice as a frequent terminal condition in cases of long duration," and also: "Jaundice is not an infrequent accompaniment of the late stage of a long continued, gastrointestinal, thyroid crisis and is distinctly a dangerous sign. In most instances it seems to be an integral part of the syndrome and due directly to the thyroid intoxication. In all probability it is only rarely due directly to cholelithiasis or an independent biliary infection, although such conditions, if present, may be lighted up and rendered acute." Similarly, Crotti⁹ may be quoted: "In a few cases of very severe thyrotoxicosis, icterus may be observed. This icterus is rare, although it is not uncommon to observe a yellowish tint of the sclerotics in severe thyrotoxic gastrointestinal disturbances. The prognosis of this icterus is always bad."

Heilmeyer¹⁰ found that among 101 cases of exophthalmic goiter in his own clinic, six showed icterus that could not be explained upon any other basis. These were usually the more severe cases and one proved fatal.

As to our own material, 35 cases were chosen from those used in the morphological section of this paper as having satisfactory histories for the investigation of this point. In eight of the 35 there was some reference to jaundice varying from slight to marked.

Various other references to the occurrence of icterus may be found in Section IV, dealing primarily with the morphological changes in the liver.

Of special interest are those cases in which the evidences of a degenerative hepatitis are so marked as to lead to a diagnosis of acute yellow atrophy. An example of this type was reported by Kerr and Rusk¹¹ in 1922. Their patient, a male, 39 years old, had presented the signs and symptoms of hyperthyroidism for a number of months. Failing appetite, nausea and vomiting were followed by deepening icterus, extreme weakness, cardiac palpitation, diminished liver dullness, bile pigment in the urine, a semicomatose state and finally convulsive movements of the extremities.

Tyrosin and leucin were not found in the urine. (The gross and microscopical appearances of the liver of this patient will be presented in the appropriate section.) Similarly, Raab and Terplan¹² described the clinical course of a female patient, 29 years of age, who showed jaundice relatively early in the course of exophthalmic goiter. Uncontrollable vomiting developed, with marked tachycardia and cardiac irregularity. Death occurred in coma. A diagnosis of subacute liver atrophy was made.

It is clear that such cases as the two just quoted differ only in degree from those characterized by icterus of but the slightest degree. This conception of a continuous series of parenchymatous changes of varying severity is of service in understanding the lesions found in the livers of the patients in our series.

II. STUDIES OF HEPATIC FUNCTION IN EXOPHTHALMIC GOITER

The functional activity of the liver in clinical hyperthyroidism has been repeatedly the subject of investigation. Certain of these researches were inspired by clinical observation of impaired function in such patients, made manifest usually by icterus, as described in the preceding section.

Hirose,¹³ in 1912, reviewed the literature showing that the threshold of galactose utilization without galactosuria is lowered by hepatic cirrhosis and catarrhal jaundice. His results supported his earlier work, and in addition he found that in patients with exophthalmic goiter he obtained his highest values for alimentary galactosuria. Strauss,¹⁴ also, discussed the occurrence of glycosuria in exophthalmic goiter and the low threshold of tolerance to galactose in patients with morbus Basedowii.

In 1922, Sanger and Hun¹⁵ compared the blood sugar curves of normal persons with those suffering from exophthalmic goiter. They confirmed the occurrence of abnormal curves in the latter group and concluded that "the increased utilization of carbohydrate after carbohydrate ingestion, along with the maintained high blood sugar, points toward an inability to store glucose—most probably a failure of liver storage, *due to some toxic change in the liver caused by the disease*. [Italics not in original.] This fits in with the results found in thyroid-fed animals, and is suggested by clinical cases of exophthalmic goiter in which carbohydrate restriction is attempted."

Youmans and Warfield¹⁶ (1926) attempted functional liver tests upon 44 patients with thyrotoxicosis. Frank jaundice or subicteric tint was noted in seven of the 44. Functional efficiency of the liver was determined by the Rosenthal modification of the phenoltetrachlorophthalein test, and in a few instances by other methods. A retention of 3 per cent or more of the dye in the blood serum at the end of one hour was considered evidence of impaired function. In 28 of the patients, tests of the glucose tolerance were made also. Twenty-two, or 50 per cent, of the patients in the entire series, showed an impairment of liver function according to the tests used. Twenty-two of the 27 satisfactorily tested showed a decreased glucose tol-

erance. These authors concluded: "It is probable, therefore, that a change in thyroid activity in thyrotoxicosis may result in a glycogen free or poor liver, more susceptible to damage by some toxic agent present in this disease, or more susceptible to injury by the disturbed thyroid function itself." This conception is not necessarily in contradiction to the generalization of Pende¹⁷ (1928) to the effect that liver function in respect to urea formation, glycogen fixation and mobilization, de-aminization, cholesterol metabolism, and bile production is decreased with decreased thyroid activity and that in *Basedow's disease a condition of hyperfunction of the liver exists*.

Kugelman¹⁸ in 1930, reviewed the rapidly increasing literature upon the disturbances in carbohydrate metabolism in exophthalmic goiter and reported the results of further studies of the blood sugar curves of normal and exophthalmic individuals following the feeding of levulose. He concluded that the thyrotoxic liver not only suffers severely as a depot for stored glycogen, but also has lost the capacity to transpose large amounts of levulose to dextrose and to store it. Thus the functional disturbance includes an intermediary phase in carbohydrate metabolism.

So constant are the changes in carbohydrate metabolism in exophthalmic goiter as evidenced by the discharge of glycogen from the liver, that this reaction has been made the basis of a biological test for thyroxin¹⁹ and for hyperthyroidism,²⁰ using the liver of the mouse as the test object. Himmelberger²¹ modified the technic of the mouse test and showed that the urine as well as the blood serum of patients with Graves' disease contains a substance capable of disturbing liver function when injected into mice.

In other respects, as well, there is evidence of disturbed liver function in patients with Graves' disease. Heilmeyer¹⁰ (1931) found the urobilin quotient (urine urobilin/stool urobilin) to be elevated in half of six cases investigated. As tested by the method of v. Bergmann and Eilbott, the bilirubin-eliminating power of the liver was impaired in each of a group of five cases. This he believed to be due to a toxic injury of the liver dependent upon the thyroid hormone, and not to circulatory insufficiency.

Lichtman² found that the galactose tolerance test gave no indication of a disturbance of hepatic function in a series of patients with uncomplicated hyperthyroidism. Likewise, he found little evidence of appreciable disturbance of the excretory functions of the liver as determined by studies on the icterus index, bilirubinemia, urobilinuria and urobilinogenuria. However, "a disturbance in the oxidation of cinchophen has been demonstrated in 16 of 20 cases of uncomplicated hyperthyroidism. Thirteen of these cases showed an increased excretion of oxy-cinchophen in the urine up to 150 mg. daily. Larger amounts, between 150 and 200 mg., or from 31 to 42 per cent of the standard test dose, were excreted in the remaining three cases. On the basis of previous experience, this is believed to indicate moderate impairment of the capacity of the liver cell to oxidize this substance further. In no instance was severe impairment of hepatic function noted.

"There was no apparent relationship between the degree of functional impairment of the liver and the basal metabolic rate, the known duration of the disease, or the percentage of weight lost. In individual cases, however, there appeared to be a tendency for the function of the liver cells to improve as the basal metabolic rate returned to normal.

"The constancy of depletion of glycogen in the liver cells in animals that have been fed thyroid substance and probably in clinical thyrotoxicosis suggests that the disturbance in oxidation of cinchophen is related to the capacity of the cells to store and mobilize glycogen."

III. EVIDENCES OF HEPATIC DYSFUNCTION IN EXPERIMENTAL HYPERTHYROIDISM

In this section will be reviewed the evidence to which Lichtman referred in the quoted paragraph preceding, that which indicates an alteration in liver function in animals to which thyroid substance or thyroxin has been administered.

In 1905, Schryver²² found that the livers of thyroid-fed animals showed a greater degree of autolysis after 24 hours than those of the non-thyroid-fed control animals. However, when thyroid had been fed for eight days or more, an opposite effect was observed.

A large proportion of the studies in this field have dealt with carbohydrate metabolism. Cramer and Krause²³ showed in 1913, that when small amounts of fresh thyroid gland are administered for two to three days to rats or cats fed on a carbohydrate-rich diet, the liver will be found to contain only traces of glycogen. This effect they found to be due to an inhibition of the glycogenic function of the liver, and not to an increased utilization of carbohydrates. It was not accompanied by glycosuria. Parhon,²⁴ Kuriyama,²⁵ and Fukui²⁶ all found the hepatic glycogen greatly diminished in experimental hyperthyroidism. Kuriyama found that in fasted rats the liver glycogen reappeared abundantly after the ingestion of a comparatively small amount of food. If a sufficiently large amount of food were administered to thyroid-fed rats, liver glycogen might sometimes reappear to a limited extent, but the quantity of glycogen so stored was much smaller than that in fasted rats which had received food with a fuel value several times less.

With pure thyroxin, and also with liver extract, Reinwein and Singer²⁷ demonstrated an increased use of O_2 by living liver cells when these substances were applied to them in concentrations of 10^{-8} to 10^{-11} . An inhibiting effect was noted at a concentration of 10^{-5} .

Dresel, Goldner, and Himmelweit²⁸ concluded that only to a slight degree, if at all, does thyroxin have a direct effect in inciting tissue oxidation. After injection of thyroxin, split products derived from proteins appear in the liver in increased amount; and it is these, and especially tyrosin, they believe, which are responsible for the elevated rate of oxidation. With

this conclusion these authors felt that they had demonstrated a *circulus vitiosus* in that thyroxin leads to an increased output of tyrosin; and tyrosin in turn, combining with iodine in the thyroid, builds thyroxin.

Under prolonged thyroid feeding other changes take place in the liver which quantitatively more than offset the loss of weight due to the lack of glycogen. This was shown by Simonds and Brandes²⁹ who rendered dogs thyrotoxic by heavy thyroid feeding for periods varying from 32 to 100 days. In these dogs the actual liver weight was in every instance greater than the theoretical liver weight as calculated for the final body weight. The mean difference was 26 per cent greater, although the mean loss of body weight was 31 per cent. In contrast, in the animals suffering from inanition, but not thyrotoxic, the actual weight of the liver was less than the calculated value with but a single exception. These authors suggested that increased functional activity and increased rate of blood flow might explain the failure of the livers of thyrotoxic animals to lose weight to the expected degree, resulting in a relative, if not an actual, hypertrophy. In this connection it may be noted that Hewitt³⁰ found that the liver was frequently hypertrophied in white rats which had received 0.1 gm. or more of fresh thyroid substance per day. These results were in accord with those of Hoskins³¹ who, two years before, had found that in thyroid-fed albino rats the liver was relatively considerably heavier than in the controls. Females showed an increase in the absolute weight of the liver of 26.7 per cent and 30.5 per cent for the older and younger groups respectively, and males showed increases of 24.4 per cent and 6.4 per cent in the corresponding groups.

IV. STRUCTURAL CHANGES IN THE LIVER IN HYPERTHYROIDISM

The clinical observations of icterus in patients with exophthalmic goiter, the results of testing hepatic function in such patients, and evidences of hepatic dysfunction or hyperfunction in experimental hyperthyroidism, as reviewed in the three sections preceding, presage the occurrence of demonstrable structural changes in the liver under such circumstances. Experimental evidence of such, as well as descriptions of hepatic changes in human material, are afforded by the literature.

Hepatic Lesions in Experimental Hyperthyroidism. In addition to the examples of actual or relative hypertrophy of the liver in experimental animals fed thyroid substance, as noted in the preceding section, there are but few references to changes in the liver in the experimental group. Farrant³² stated that the livers of cats and rabbits, fed thyroid gland, showed fatty degeneration, most marked around the centers of the lobules. In a study directed especially toward the heart in experimental hyperthyroidism, Hashimoto³³ found parenchymatous degeneration of the liver cells about the efferent veins, varying from "fatty degeneration" to necrosis. These changes were sometimes found throughout the lobule, but were never confined to the periphery. Hypertrophy of liver cells, mitotic figures and

double nuclei were found in the peripheral zones. While the evidences of chronic passive congestion coincided with marked myocardial changes, the parenchymatous degeneration did not.

Gross and Microscopical Changes in the Liver in Exophthalmic Goiter. In 1880, Eger⁴ gave a detailed history of a case of hyperthyroidism in which icterus of the conjunctiva and skin had been noted. At autopsy the liver was found to be atrophic, the left lobe having the appearance of being but an appendage to the right. The parenchyma was saffron-yellow grossly, and microscopically showed lipoidosis, with intact liver cells remaining only in areas. Farner³⁴ mentioned "atrophic cirrhosis of the liver" in his Case I, and "marked atrophic cirrhosis" in Case IV. This patient showed an icteric coloration of the skin and body fluids. Cirrhosis hepatitis was recorded by Askanazy³⁵ in a patient with slight icterus in the course of exophthalmic goiter. In a second case the anatomical diagnosis was an atrophic, cyanotic nutmeg liver. Microscopical findings for these two were not given. In a third case the liver was described as an atrophic, cyanotic nutmeg liver with an area of coarse lobulation and fatty change, but in the microscopical description only a central cirrhosis was mentioned.

Although our own observations were made in the course of routine autopsies, and without reference to any previous description, search of the literature reveals several references to precisely the same type of interlobular hepatitis as that to be described, in association with exophthalmic goiter. I quote (in translation) from Dinkler's³⁶ description of the liver in his first case: "The liver showed a considerable accumulation of fat droplets in the peripheral cells of certain acini; in the cells of the central regions only by means of the method of Marchi was it possible to demonstrate a deposit of very finely divided fat. In individual areas there were found in the septa of Glisson's capsule submiliary cell-collections, of which the unit elements were in part round and in part oval cells, separated one from another by a fibrillar intercellular substance."

Marine and Lenhart³⁷ wrote: "In a significant number of the long-standing cases [of exophthalmic goiter] coming to autopsy, cirrhosis of the liver has been observed. In the gross such livers are reduced in volume, sometimes smooth, sometimes slightly granular and again distinctly hobnailed. The extent of the connective tissue increase varies from a slight thickening of the portal spaces to well-marked fibrous bands. The liver-cells usually exhibit some degree of fatty metamorphosis." In four of six cases coming to autopsy at Lakeside Hospital, a diagnosis of atrophic cirrhosis was made.

Landau³⁸ found in some cases cirrhotic livers which had not been diagnosed during life. Histologically, this lesion was easily differentiated from stasis-induration. Thus he felt that it must be referred to a toxic etiology.

Although particularly concerned with alterations in the islands of Langerhans, Pettavel³⁹ gave a very good description of changes in the liver

in certain of his cases of exophthalmic goiter. Of the liver of his third case he stated that the connective tissue of the extensions of Glisson's capsule was increased in a patchy manner between the acini. In the increased connective tissue there was a slight lymphocytic infiltration. Rarely the spreading growth of the connective tissue became confluent so that small islands of liver tissue were entirely enclosed by it. New-formed bile ducts were not seen. In the fourth case, also, he referred to the localized interstitial hepatitis, but this case was complicated by miliary tuberculosis. Also Rautmann⁴⁰ described a local increase in the periportal connective tissue, with lymphocytic infiltrations. Such changes he attributed in part to long sustained stasis-hyperemia and in part to preëxisting complications (cirrhosis). Yet he recognized a double etiology—circulatory and toxic—for the lipoidosis of the liver cells. The cirrhotic changes in the liver are mentioned also by Holst,⁴¹ who referred to the frequency of urobilinuria in patients with exophthalmic goiter.

Assmann,⁴² whom Lichtman² followed closely, postulated four groups of patients who might show icterus in coincidence with exophthalmic goiter. In the second group he placed those depending upon cardiac insufficiency. Yet he illustrated this group by a case in which the liver showed, in addition to high grade lipoidosis, localized atrophy of the lobules. At the periphery of the atrophic lobules there were increased interstitial connective tissue, infiltration with round cells and slight bile duct proliferation. These changes are not those resulting from chronic passive congestion or stasis. In a third group Assmann placed those cases, chiefly with severe general toxicosis and rapidly lethal outcome, which in the more severe form pass over into an acute yellow atrophy. These he believed to be very probably related etiologically to the hyperthyroidism. The two patients used to illustrate this group both survived so that examination of liver tissue was not possible.

The first clinical observation of a condition which might properly be considered acute yellow atrophy in association with exophthalmic goiter was that of Kerr.^{11, 43} His patient was a male, age 39, who first showed icterus on the fourteenth day following a bilateral partial thyroid lobectomy for hyperthyroidism. Liver dullness was diminished and bile was present in the urine. Death occurred two days later. At autopsy a diagnosis of "hyperplastic goiter with chronic interstitial strumitis" was established. The liver weighed 1290 gm. Its surface was coarsely granular and of light brownish red color. On section, the normal structure was obscured and the color was an opaque reddish-brown with numerous scattered hemorrhagic blotches. On microscopical examination there was almost complete loss of the normal architecture. In the periportal regions there was a marked diffuse infiltration with lymphocytes and some plasma cells. Beyond [central to] these lymphocytic masses were areas showing the remains of necrotic liver cells, infiltrating lymphocytes and leukocytes and hemorrhage. The illustrations accompanying the description show a very extensive necrosis of the parenchyma and fully justify the clinical diagnosis.

In the year following the first report by Kerr, Raab and Terplan¹² described a similar instance under the title of "Basedow's Disease with Subacute Yellow Atrophy." Loss of weight, weakness, vomiting, rapid and sometimes irregular pulse, and icterus had marked the clinical course. The liver weighed 1160 gm. Consistency was reduced; the cut surface was diffusely yellow with dark red areas, and the periportal and interacinar connective tissue stood out in relief. Microscopical examination showed extensive necrosis, lipoidosis, deposits of bile pigment, and localized infiltrations of round cells and leukocytes in the necrotic areas. Fibroblastic proliferation and new-formed bile ducts gave evidence of attempted repair. The entire picture was that which may properly be called subacute acute-yellow-atrophy of the liver.

Barker,¹⁴ also, has described atrophy and necrosis of the liver in connection with a severe thyro-intoxication.

V. THE HEPATIC LESIONS IN A SELECTED SERIES OF AUTOPSIES UPON PATIENTS WITH EXOPHTHALMIC GOITER

In the course of routine histological examination of autopsy material from patients who have shown the clinical and histopathological evidence of exophthalmic goiter, such retrogressive changes in the liver as simple and pigment atrophy, cloudy swelling, and particularly degenerative fatty infiltration are noted frequently. It is impossible to attach specific significance to such changes because of their very frequent occurrence in a large number of conditions other than thyrotoxicosis. Many patients with Graves' disease have been operated upon recently and anesthesia alone may cause degenerative fatty infiltration of the liver. While a thyrogenic origin for such acute degenerative processes is not at all unlikely, there is at present no method available for proving that such is the case. These changes are probably expressive of rather temporary states in the constantly varying and probably often abnormal metabolism of the liver cells.

To a lesion of another type which has been noted from time to time, and to which reference has already been made in the survey of the literature, no such transient character can be attributed. This lesion can best be designated as a *patchy chronic parenchymatous interlobular hepatitis*. In its slightest form this is made known by a slight enlargement of the islands of Glisson (portal canals) with lymphocyte infiltration. In more marked degrees there is a notable increase in the connective tissue, which enlarges the islands so that the liver lobules tend to be encircled by this increased fibrous connective tissue and isolated one from another as in atrophic cirrhosis. From the usual form of atrophic cirrhosis, this lesion differs in being irregularly distributed through the substance of the liver, many islands escaping entirely. Also, when present to a marked degree, there is a slight intralobular invasion at the periphery of the lobules. As compared to atrophic cirrhosis these lesions show less bile duct proliferation in the increased stroma, although some new formation of bile ducts is always present

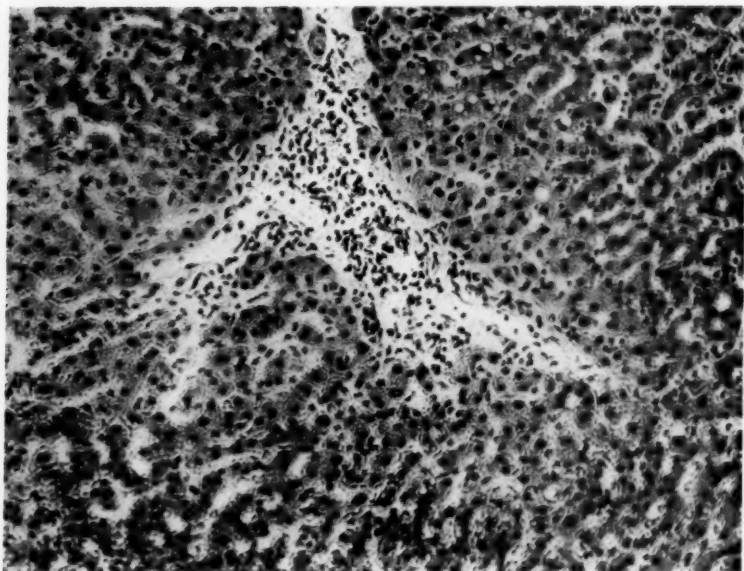


FIG. 1. Interlobular hepatitis of slight degree. Slight fibrosis and lymphocytic infiltration. This and the following photographs are from the livers of patients with exophthalmic goiter.

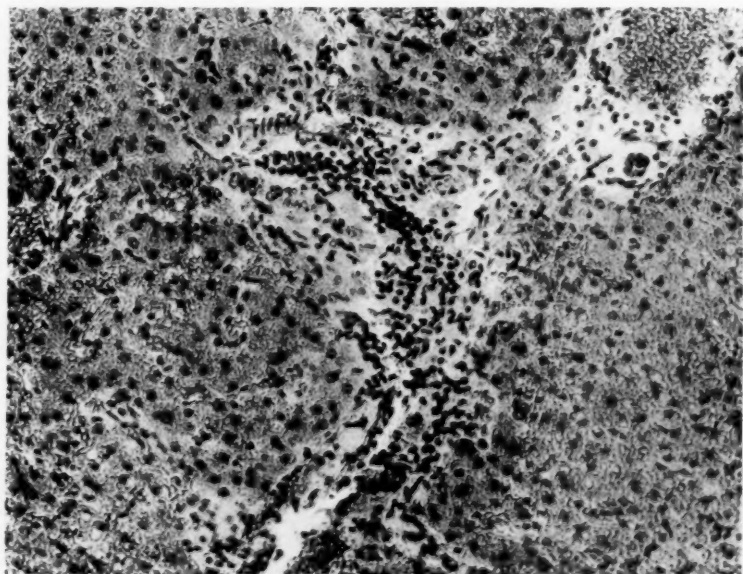


FIG. 2. Slightly more marked degree of chronic hepatitis than in the preceding figure. Slight bile duct proliferation as well as fibrosis and lymphocytic infiltration in an island of Glisson.

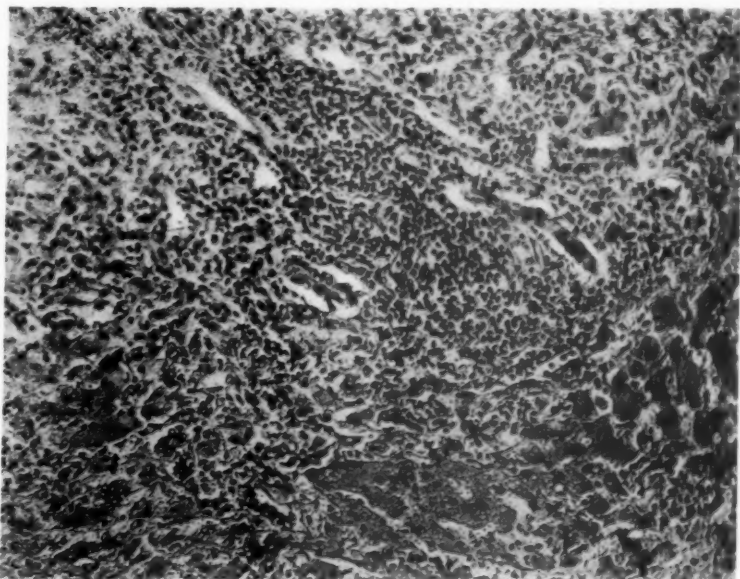


FIG. 3. Well marked and active chronic interlobular hepatitis. Heavy lymphocytic infiltration. Inflammatory process encroaches upon the peripheral zone of the lobules.

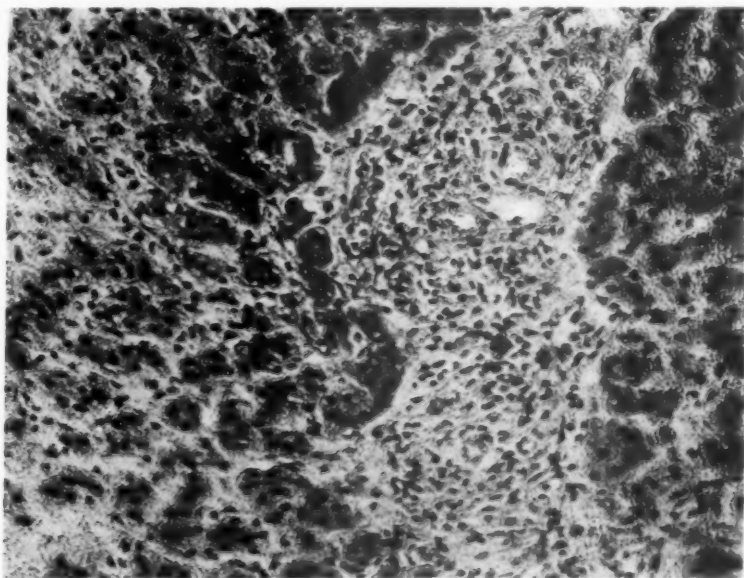


FIG. 4. Fibroblastic proliferation and moderate lymphocytic infiltration of the portal canal. A less active and presumably older process than that shown in figure 3.

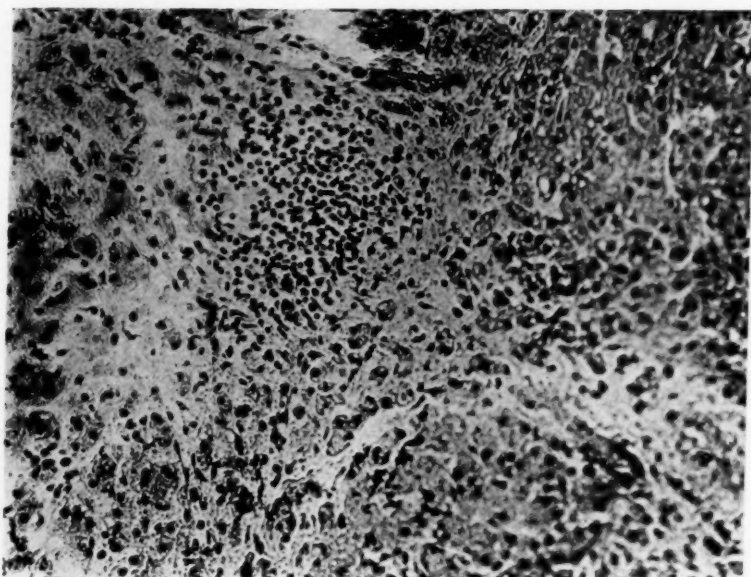


FIG. 5. Extensive development of stroma in an island of Glisson. Marked infiltration with lymphocytes. Degenerative fatty infiltration of the neighboring liver cells.

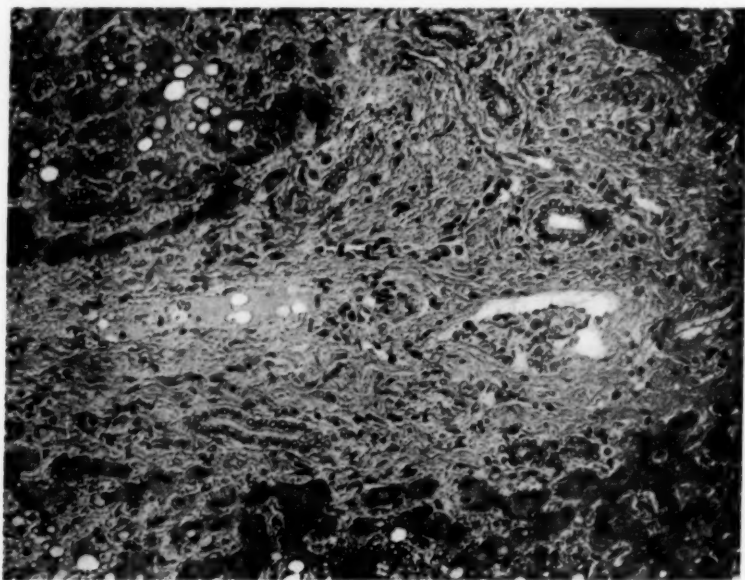


FIG. 6. Older residual fibrosis greatly enlarging the island of Glisson. Increased bile ducts.

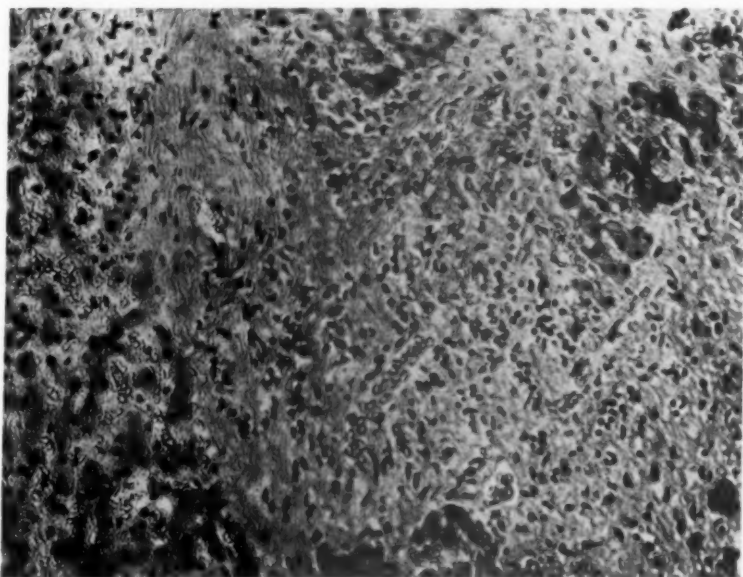


FIG. 7. Marked chronic parenchymatous hepatitis from a patient with Graves' disease. Widespread fibrosis, slight bile duct proliferation and diffuse lymphocyte infiltration.

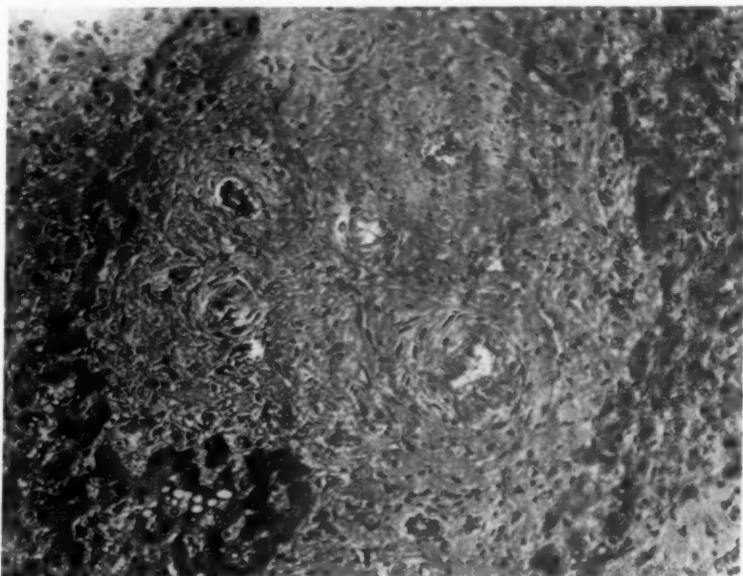


FIG. 8. Old residual fibrosis in an island of Glisson. This shows well the concentric fibrosis frequently seen about the blood vessels of the portal canals.

when the islands are greatly increased in size. In an older but not necessarily more extensive stage, the connective tissue may be moderately hyaline in the greatly increased portal canal, and the lymphocytic infiltration reduced to a minimum. Rarely are livers seen with areas of necrosis still present in the parenchyma, but the extensive patchy fibrosis encountered more frequently, having small groups of liver cells scattered through it as in advanced atrophic cirrhosis, may well represent a region in which necrosis has been present. Variations in the extent and age of this form of interlobular hepatitis are shown in figures 1 to 8, all of which are taken from cases used in the series under consideration.

From the microscopical description and the illustrations it will be apparent that this lesion cannot be recognized by the methods of gross pathology when present in the lesser degrees. When more marked the appearances are those of a more or less localized atrophic cirrhosis, a diagnosis which has rather frequently been assigned to such livers as already pointed out in the preceding section of this paper.

Having observed this form of chronic parenchymatous hepatitis in association with exophthalmic goiter in a number of instances, it appeared that there might be a significant correlation between the two conditions. However, impressions thus gained are apt to be deceptive, for when interest is once aroused, the occurrence of the anticipated phenomenon usually carries more weight in memory than its absence. It therefore became desirable to undertake, as far as was possible, a controlled study of the coincidence of such liver changes with exophthalmic goiter. The method of parallel series seemed the only suitable approach.

From a series of 61 autopsies upon patients who had had undoubted clinical manifestations of exophthalmic goiter with the diagnosis verified by microscopical examination, or whose thyroids gave definite histological evidences of that disease even though the clinical diagnosis had not been fully established before death, all were eliminated in which factors known to be significant in the production of hepatitis were present. Thus one or more cases were eliminated for each of the following: latent syphilis, acute and chronic cholecystitis, cholelithiasis, leukemic infiltrations and toxemia of pregnancy. This left a final group of 48, in respect to each of which no known cause of hepatitis existed other than the possibility that it might be due to thyrotoxicosis.

Since chronic hepatitis, particularly in a minimal degree, is occasionally encountered without known cause in the livers of patients who have not had Graves' disease, it became necessary to establish a further control of the selected material. This was done by matching each patient with another of the same sex and of approximately the same age, excluding the same group of conditions known to produce pathological changes in the liver, but also excluding Graves' disease. The incidence of chronic hepatitis was then ascertained in the two series with the following result:

	Graves' disease	Control series
No chronic hepatitis	6	33
Slight chronic hepatitis	16	14
Well-marked chronic hepatitis	26	1
	<hr/> 48	<hr/> 48

Care was taken to use the same standards throughout. Chronic hepatitis of slight degree occurred with approximately the same frequency in both series. Under this heading were placed all livers showing a slight increase in size of the portal canals with small infiltrations of lymphocytes. It is doubtful whether a reaction of this degree can be considered of significance in the present investigation. In the Graves' disease series but six were without hepatitis, while this was true of 33 of the control series. On the other hand 26 of the Graves' disease series showed a well-marked chronic hepatitis as compared to one in the control series. (This single case may have some special interest. Review of the protocol showed that this patient, whose death was caused by a pituitary tumor, had a well-marked hypoplasia of the adrenals. Since adrenal hypoplasia is of constant occurrence in individuals with the Graves' constitution, there may be a significant relationship involved.)

Such a marked difference in the occurrence of hepatitis in the two series seems to establish the fact that a definite significance attaches to the coincidence of Graves' disease and chronic interlobular hepatitis of the type described. Whether a direct or indirect causal relationship exists between them cannot be answered with certainty at the present time. It is not unreasonable to surmise that the same active principle, which in small amounts increases the metabolic activity of the liver and leads even to hypertrophy of the organ, and in somewhat larger amounts causes the discharge of stored glycogen and inhibits glycogenic function, may in still larger amounts prove actively destructive, producing localized degenerative changes and even necrosis. Furthermore, it is easy to reconcile the cirrhotic effect of such an agent acting in a moderate degree for a prolonged period with the actively necrosing effect observed in those examples of exophthalmic goiter in which the clinician, properly enough, has made a diagnosis of acute yellow atrophy of the liver. Thus it seems probable that the patchy interlobular hepatitis found associated with Graves' disease, like the more or less similar forms of chronic hepatitis of which the etiology is known, is directly or indirectly of toxic origin. The suggestion that this hepatitis is of circulatory origin can be dismissed by calling attention to its peripheral position in the lobule. Chronic passive congestion, "nutmeg liver," asphyxiative central necrosis, or even a so-called central cirrhosis may be present without in any way resembling or creating confusion with the island changes and peripherally encroaching hepatitis found in so many of the patients with Graves' disease.

It is not within the scope of this paper to undertake an analysis of the

very difficult question as to whether there is a correlation between the extent and severity of the liver changes and the general intensity of thyrotoxicosis as gauged by clinical standards. There is some evidence to show that such a correlation exists, particularly in those cases in which there are evidences of extensive damage to the liver parenchyma.

SUMMARY

That the liver may be, and frequently is, involved in Graves' disease is shown *clinically* by the occasional occurrence of icterus, marked degrees of which are known to be of serious import in this disease; *physiologically*, by the accumulating evidence of altered liver function in such patients; *experimentally*, by the evidence of hepatic dysfunction following administration of thyroid substance and thyroxin, and *morphologically*, by structural changes in the liver, varying from slight degrees of chronic hepatitis to a widespread degenerative and necrotizing process which must be considered an "acute yellow atrophy." In a series of 48 carefully selected cases of Graves' disease, well-marked hepatitis was found in 54 per cent; while a matched control series of the same size yielded but a single case (2 per cent) with well-marked hepatitis. As usually seen, this liver lesion is interlobular, is patchily distributed, involves the peripheral portion of the lobules to a moderate degree, and shows relatively more fibrosis and lymphocyte infiltration than bile duct proliferation. It may be characterized as a *patchy chronic parenchymatous interlobular hepatitis*. Correlation with the severity and duration of thyrotoxicosis is indicated, but as yet unproved.

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A PAINLESS HISTAMINE SKIN TEST: AN EXPERIMENTAL STUDY *

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IN 1927 Thomas Lewis¹ demonstrated that the histamine skin reaction consisted of three distinct factors, (1) a local dilatation of the capillaries, venules, and arterioles by direct action which caused a purplish areola, (2) a local increase in the permeability of the walls of the minute vessels by direct action, which caused a wheal at the site of the injection, and (3) a widespread dilatation of the surrounding arterioles by local reflex action, which was visible as a red flare. He also demonstrated that if the circulation was cut off completely a purple spot would appear but no wheal or flare, and that coldness of the skin retarded the reaction. In 1928 Starr² used this test in a study of peripheral circulation in diabetics. Using the method of pricking the skin through a drop of histamine, he found that the changes suggesting a reduction in circulation were (1) delay in the appearance of the reaction, (2) delay in the appearance plus a reduction of the intensity of the reaction, (3) failure of either flare or wheal to appear, (4) failure of both the flare and the wheal to appear and the reaction to consist of only a purple spot which was a sign of complete obstruction of arterial circulation. With this method of performing the test, Starr found that normally the reaction was at its height in two and one-half to five minutes.

De Takats³ modified the method of performing the test, and instead of puncturing the skin through a drop of histamine he injected 0.1 c.c. of 1:1000 histamine solution intradermally. The reactions by this method are the same as those described by Starr. The areola is a narrow purplish border about the site of the injection. The wheal is irregular but sharply defined and is usually one-half to one centimeter in diameter. The flare surrounding it is also irregular but is not raised and extends for one to two centimeters in each direction. In the Peripheral Circulatory Clinic of the Michael Reese Hospital our experience has been that the reaction is more intense and easier to read when the histamine is injected intradermally than when the skin is pricked through a drop of the solution. The test is fairly accurate as a means of determining circulatory efficiency and agrees closely with the oscillometric readings and the skin temperatures. Besides diminution in circulation other factors which cause a delayed or absent reaction are degeneration of cutaneous nerves, previous use of histamine in the same spot, injury of the skin by ultra-violet and roentgen-ray or burns, and various skin diseases.

One of the great faults of the test when performed by the method of intradermal injection is its painfulness. Although the pain lasts only a

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From the Peripheral Circulatory Clinic of the Michael Reese Hospital.

TABLE I

Because 1 : 1000 histamine solution was the standard used in the Peripheral Circulatory Clinic, its reactions were graded ++++ in this series of tests. A ++++ areola is one $\frac{1}{8}$ to 1 mm. wide about the primary wheal made by the injection. A ++++ wheal is the irregular secondary wheal 4 to 5 mm. in diameter. A ++++ flare is one 2 cm. to 3 cm. in diameter and of intense pink color.

Solution	Pain	Areola	Wheal	Flare	
				5 Min.	10 Min.
1 : 10000 Histamine					
1 : 2000 "	+	+	+	+	+
1 : 1000 "	+	+	+	+	+
2 : 1000 "	+	+	+	+	+
4 : 1000 "	+	+	+	+	+
$\frac{1}{2}\%$ Novocaine	+	+	+	+	+
1 $\%$ "	0	+	0	0	0
2 $\%$ "	0	+	0	0	0
4 $\%$ "	0	+	0	0	0
1 : 2000 Histamine in $\frac{1}{2}\%$ Novocaine	+	+	+	+	+
1 : 2000 "	+	+	+	+	+
1 : 1000 "	+	+	+	+	+
1 : 1000 "	+	+	+	+	+
1 : 1000 "	+	+	+	+	+
2 : 1000 "	+	+	+	+	+
2 : 1000 "	+	+	+	+	+
2 : 1000 "	+	+	+	+	+
Needle prick through 1 : 1000 histamine	0	+	+	0	+

TABLE II

The tests were made simultaneously, 1 : 1000 histamine being used on the lateral side and 1 : 2000 histamine in $\frac{1}{2}$ % novocaine on the medial side of the extremity.

Case	A.M.	D.F.	C.C.	I.M.	I.M.
Diagnosis	Thromboangiitis Obliterans				
Extremity					
Solutions	Left Lower		Right Lower		Left Lower
	$\frac{1}{1000}$ Hist.	$\frac{1}{2000}$ Hist. $\frac{1}{2}$ % Novo.	$\frac{1}{1000}$ Hist.	$\frac{1}{2000}$ Hist. $\frac{1}{2}$ % Novo.	$\frac{1}{1000}$ Hist.
5 Min.	++ ++ 0	++ ++ 0	++ ++ 0	++ ++ 0	++ ++ 0
10 Min.	++ ++ ++	++ ++ ++	++ ++ ++	++ ++ ++	++ ++ ++

second or two, its excruciating sharpness frequently gives rise to bitter complaints on the part of the patient, especially when it is necessary to repeat the tests at intervals to note changes in peripheral circulation. The work here reported was undertaken with a view to establishing some modification of the test which would be as rapid and as accurate as the 1:1000 histamine intradermally but not as painful. Various dilutions of histamine alone and in combination with novocaine were tried. In table 1 is a list of solutions used and of the results obtained. The tests were performed on the volar surface of the forearm of a normal subject. In each case sufficient solution was injected intradermally to make a primary wheal 2 mm. in diameter and the pain due to the insertion of the needle was discounted.

A study of the table reveals that the size of the reaction and the intensity of the pain vary directly as the concentration of the histamine when used alone. To prevent the pain, correspondingly stronger solutions of novocaine are necessary. The combinations which gave excellent histamine reactions without pain were 1:2000 histamine in $\frac{1}{2}$ per cent, 1 per cent and 2 per cent novocaine, 1:1000 histamine in 1 per cent and 2 per cent novocaine and 2:1000 histamine in 2 per cent novocaine. Although the stronger solutions of histamine gave more rapid and more intense reactions the severe inflammatory changes that they induce constitute a serious objection. When 2:1000 histamine and 4:1000 histamine solutions were used, alone or with novocaine, a hemorrhagic inflammatory area was formed at the site of the injection which persisted for several days. As these severe reactions were obtained in normal skin, one can readily see the danger of using such strong solutions of histamine in testing skin with deficient circulation. In such cases it is best to use the weakest solutions which give good reactions.

We have found that 1:2000 histamine in $\frac{1}{2}$ per cent novocaine is such a solution. The test is painless and the reaction in the skin is intense and rapid enough to be practical. To determine the efficiency of this solution in skin with deficient circulation a few such cases were tested. (Table 2.) There was no noticeable difference between the reactions following injections of 1:1000 histamine and those produced by 1:2000 histamine in $\frac{1}{2}$ per cent novocaine.

The results of this series of tests showed that skin with deficient circulation reacted as intensely to 1:2000 histamine in $\frac{1}{2}$ per cent novocaine solution as it did to 1:1000 histamine alone. In both cases the height of the reaction was reached in 10 minutes.

CONCLUSION

A painless but efficient histamine skin reaction may be obtained by injecting intradermally 1:2000 histamine in $\frac{1}{2}$ per cent novocaine solution. The reaction may be read at five minutes but is best read at 10 minutes when it is at its height.

The author wishes to thank Dr. Ralph B. Bettman and Dr. Samuel Soskin for suggesting this research.

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INTRAVENOUS VACCINE THERAPY IN CHRONIC ARTHRITIS * †

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MUCH attention has been focused on the subject of chronic arthritis during the past few years and a survey of the literature shows an increasing belief in the streptococcal etiology of this condition.^{1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11}

Many points of similarity have been noted between chronic arthritis, especially the so-called rheumatoid type, and rheumatic fever.¹² Menzer,¹³ in 1902, in an endeavor to explain the peculiar action of his serum in rheumatic fever, advanced a theory which, in many respects, resembles the modern concept of allergy. More recently, Swift^{14, 15, 16, 17} and Zinsser^{18, 19} have brought forth evidence that the pathogenesis of rheumatic fever can be explained by the existence in certain individuals of a condition of hypersensitiveness (allergy or hyperergy) to streptococci, resulting from repeated low grade infection or from the persistence of foci of infection in the body. This hypothesis has been applied in a measure also to chronic arthritis. Cecil⁷ believed that bacterial allergy might or might not influence the clinical picture of chronic arthritis.

Experimental investigations by Swift et al.^{20, 21, 22, 23} on the reactions of animals to infection with streptococci under various conditions, have shown that the reactive state of these animals was conditioned largely by the mode of inoculation. When made directly into the tissues, the resulting state was that of hyperergy but when the preliminary inoculation had been made intravenously, the resulting state was one of immune hyposensitivity. It has been shown^{15, 21} that hypersensitive animals can be rendered immunely hyposensitive by suitable intravenous vaccination.

Assuming that hyperergy played a rôle in chronic arthritis and reasoning that the hypersensitive state might be influenced, as shown by Swift in animal experimentation, we were prompted early in 1930 to study the effects of the intravenous use of phenolized, unheated, autogenous vaccines prepared from organisms with high agglutinin titers. The necessity of

* Presented as a Clinic at the Montreal Meeting of the American College of Physicians, February 8, 1933.

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† While this paper was in preparation the following articles appeared:

1. CLAWSON, B. J., and FAHR, G. E.: Experiments leading to a possible basis for vaccine therapy in acute rheumatic fever, *Proc. Soc. Exper. Biol. and Med.*, 1930, xxvii, 964-965.
2. SWIFT, H. F., HITCHCOCK, C. H., DERICK, C. L., and McEWEN, C.: Intravenous vaccination with streptococci in rheumatic fever, *Am. Jr. Med. Sci.*, 1931, clxxxi, 1-11.
3. WETHERBY, M., and CLAWSON, B. J.: Chronic arthritis, with special reference to intravenous vaccine therapy, *Arch. Int. Med.*, 1932, xlix, 303-320.
4. CLAWSON, B. J., and WETHERBY, M.: Experimental basis for intravenous vaccine therapy in chronic arthritis with summary of results obtained in patients, *ANN. INT. MED.*, 1932, v, 1447-1461.

suitably controlling this work was realized. A group of patients was then selected, many of whom had previously received other types of treatment before coming under our care. No other form of medication was used. A routine clinical study, consisting of the following, was made on each patient:

1. Special history and physical examination with emphasis on evidence of existing or past rheumatic affections or other allergic phenomena.
2. Special examination by the Nose and Throat, Dental, Genito-Urinary, Gastrointestinal and Gynecological Departments.
3. Urinalysis.
4. Culture of stool.
5. Nose and throat cultures (these were repeated in the case of indefinite findings).
6. Complement fixation using a number of antigens composed of pooled strains of their respective bacterial groups.
7. Sedimentation rate.
8. Agglutination reactions with autogenous organisms using the patient's own blood serum.
9. Basal metabolism.
10. Complete blood count.

The bacteriologic and serologic studies were made as follows:

Complement fixation reactions, and cultures of the nose, throat and feces were made on all patients. Agglutination reactions were made with all smooth strains isolated. Several reexaminations were necessary in some cases. Cultures of teeth, gall-bladder or other foci were also made where necessary. Those organisms having an agglutinin titer of 1:160 or above were considered pathogenic.

Throat swabs were incubated in Rosenow's brain heart infusion over night. The following morning they were stirred around in the medium and discarded. The cultures were then allowed to stand a few hours to permit settling of the gross particles and the floccules of rough organisms. Blood agar plates were inoculated from the supernatant fluid and incubated in Varney phosphorus jars. Some streptococci having high agglutinin titers grew poorly in aerobic cultures and successful cultures were more readily obtained in the phosphorus jars.

Each type of colony appearing on the blood agar plates was transferred to other blood agar plates in order to obtain pure cultures. Incubation in the anaerobic jars permitted a greater differentiation of the various types of colonies than was possible by the usual methods.

The pure growths were scraped from the blood agar plates and transferred to 50 c.c. bottles of Rosenow's medium. A dense growth was usually obtained over night. The growths were examined the following morning and tested for purity. Rough strains were discarded. The smooth strains were centrifuged and emulsified in 5 c.c. of 0.5 per cent phenol in normal saline. After taking a small amount for the agglutina-

tion reaction, the tubes were stored in the refrigerator for future reference.

For the agglutination reaction, a series of tubes containing about 11 c.c. of saline were placed in a rack. The heavy suspensions were added to these tubes until the density approximated 100 millions per c.c. The tubes were allowed to stand for two hours to permit the coarser particles to settle. Serum dilutions were prepared ranging from 1:40 to 1:10,240. A saline control was used. An equal volume of the decanted suspension was added to each of the tubes of diluted serum, and they were vigorously shaken and placed in the water bath at 51° C. for two hours. They were then allowed to stand over night at room temperature. Critical comparison was necessary for an accurate determination of the end-point. Those organisms having an agglutinin titer of 1:160 or over were washed a second time and preserved. The others were discarded. Each suspension was tested for sterility before being mixed with the rest of the vaccine.

The injections were given once or twice weekly. At each time the reactions following the previous injection were recorded. (See chart 1.) The same type of syringe and the same gauge needle were used and, in calculating the dose, allowance was made for the capacity of the needle.

In the beginning, patients receiving intravenous injections of vaccine were taught to take their temperature and were requested to do so at two-hour intervals during the afternoon of the day of treatment and the following day.

The reactions following the intravenous injection of vaccines were as a rule focal, rather than general in nature, the latter having been eliminated by adoption of the procedure outlined below. Other workers have used large initial doses which resulted in general reactions with elevation of temperature. This made it difficult to determine the influence of protein shock as a factor in their work, and their dosage, therefore, was not comparable with ours.

Since we were dealing with ambulatory patients who were seen for a short period once or twice weekly, the early treatments had to be instituted with considerable caution. We began by giving initial doses of 5,000 organisms, but this frequently produced a general reaction with chills and elevation of temperature. (See Case I.) In order to avoid a general reaction, it was found necessary to give an initial dose of not more than 500 bacteria. In many instances, however, it was found that this dose would produce a severe focal reaction. One ambulatory patient was confined to bed for four weeks following an even smaller dose. (See Case II.)

The average initial dose was then gradually reduced until a reaction was no longer encountered in the majority of patients. This dose was found to be about 10 to 20 organisms, depending somewhat on the severity of the disease. A few of our patients have not been able to tolerate even this small dose. They showed marked improvement, however, when the dose was further reduced to 4 or 5 organisms. In a small group of cases, a larger dose could undoubtedly have been given without producing either

a focal or general reaction, but the possibility of causing a severe focal reaction was too great to warrant such a procedure. (See Case II.) In the beginning, the dose was increased as rapidly as possible but not sufficiently to produce an elevation of temperature or a severe focal reaction. In a number of instances, however, this rapid increase was followed by premature ventricular contractions, precordial pain, severe fatigue, dizziness, sinus tachycardia, loss of weight, headaches, insomnia, extreme unexplained nervousness, disturbances in vision, diarrhea and severe mental depression sometimes simulating mild encephalitis. Regardless of these reactions, some showed improvement in the focal symptoms. (See Cases III and IV.)

CASE I

Mrs. J. L., white, female, aged 45; diagnosis, advanced rheumatoid arthritis. *Streptococcus viridans* (Brown's classification), having an agglutinin titer of 1:5120, was isolated from the throat and a vaccine made from it. An initial dose of 5,000 was given. A severe chill occurred five minutes later. Two hours later, the temperature reached 103° F. There was also a severe delayed focal reaction. Five days later, a dose of 1,000 organisms was given which was followed by a slight general reaction manifested by a slight chill and a temperature of 100.5° F. The dose was then increased to 1,000, 1,500, 2,000 and 2,500 organisms at five day intervals without any general reaction. Five days later, 4,000 organisms were given (an increase of 60 per cent). This was followed by a moderate general reaction with a chill, the temperature reaching 101° F. The dose was then repeated without any reaction. Five days later the patient received 6,000 organisms (an increase of 50 per cent) which was followed by a general reaction, the temperature again reaching 101° F. The next four doses were increased at the rate of 10 per cent with no apparent reactions. The percentage of increase was then slowly raised to 25 per cent without producing any general reaction.

This case demonstrates the difficulties encountered at the beginning of this work. It also illustrates our contention that the percentage of increase by this method should be small.

CASE II

M. G. M., white, male, aged 24; diagnosis, rheumatoid arthritis. The patient was well until June 1930, when he complained of vague pain in the left hip and both knees which gradually extended to other joints and became more severe. Roentgen-ray examination of the spine in September 1931, revealed ankylosing arthritis (Marie-Strumpell disease) involving the entire spine, also marked arthritis of both hips, wrists, fingers, etc. A hemolytic streptococcus with an agglutinin titer of 1:640 was isolated from the throat. An initial dose of 300 of these organisms was given, with no general reaction. On the other hand, there was a severe focal reaction with marked increase of pain in the right hip, sacro-iliac joints, knees, and entire spine, and the patient was confined to bed. The pain was severe and was not relieved by the usual anti-rheumatic drugs. The pain continued to be severe for two weeks, after which there was slow improvement. He was able to be out of bed four weeks from the date of the inoculation. Six weeks after the injection he had not fully recovered and had more difficulty in walking than previous to the injection of the vaccine. A dose of 10 organisms at this time did not produce a reaction. He then stated that he had previously been given vaccine treatments and usually experienced severe focal reactions. With our present knowledge of the necessity of a small initial dose, depending somewhat on the severity of the disease, we would have begun with 15 or 20 organisms.

This case illustrates the extreme type of focal reaction which may occur even with a comparatively small dose and this reemphasizes the risk of employing large initial doses.

CASE III

J. W., physician, white, male, aged 52; diagnosis, rheumatoid arthritis of five years' duration involving both feet, ankles and both hands. An alpha type streptococcus having an agglutinin titer of 1:1280, was recovered from the throat. An initial dose of 500 organisms was given which was increased about 25 per cent at four day intervals until a total of 12,000 organisms was reached. Following this dose there was dizziness, precordial pain, severe nervousness, tachycardia and insomnia. The precordial pain was occasionally severe and at other times dull and aching in character. The pain, nervousness, tachycardia and insomnia persisted for 48 hours and then disappeared. The dose was then reduced to 5,000 organisms which did not produce an untoward reaction. It was then increased to 7,000 and 8,000 organisms with no unfavorable result. Five days later, a dose of 10,000 organisms was given and this was again followed by precordial pain, palpitation, nervousness, dizziness, insomnia and fatigue. An electrocardiogram was taken at this time, and again after all symptoms of the reaction had disappeared. In the first record premature beats were observed which were no longer present when the second record was taken. The dose was reduced to 3,000 which was followed by a beneficial response. It was then increased 10 per cent each time with no unfavorable reaction, until the dose reached 14,000 organisms when the above symptoms reappeared. Since that time the focal symptoms have been markedly improved.

CASE IV

Mrs. S. R. B., white, female, aged 33; diagnosis, early rheumatoid arthritis involving the fingers of both hands, both wrists, cervical spine and both knees. The symptoms began one year before, appearing immediately after childbirth and steadily increasing. About three months before, the tonsils were removed without apparent improvement. Two infected teeth were extracted from which a smooth strain of *Streptococcus viridans* with an agglutinin titer of 1:640 was obtained and from which a vaccine was made. Cultures of the nose and throat yielded strains of *Streptococcus hemolyticus* with negative agglutinin titers. They were not used in the preparation of a vaccine as they were considered unimportant. Stool cultures were negative. Roentgenograms of the hands, wrists and fingers revealed early arthritis. An initial dose of 50 organisms of the *Streptococcus viridans* strain was given on November 13, 1931. The dose was slowly increased according to chart 1 until December 28, when 500 organisms were given. This was followed by a slight focal reaction, nervousness and marked dizziness. On January 4, the dose was increased to 700 organisms resulting in nervousness, insomnia, inability to concentrate and loss of appetite. The dose was repeated January 8 and 13. The effects were similar to those caused by the previous injection. On January 18, the patient still complained of dizziness, occasional attacks of double vision with inability to read, was very irritable, depressed and cried frequently. She also complained of palpitation and an occasional precordial pain. The vaccine was discontinued until January 28. By this time the nervousness had diminished, the dizziness had entirely disappeared, there was considerably less fatigue, less insomnia and her appetite was improved. A dose of 50 bacteria was then given which was slowly increased every four days until March 23, when it had reached 400 bacteria. This was followed by dizziness, nervousness, fatigue and insomnia. Lowering the dose was accompanied by disappearance of these symptoms. Since the patient was not receiving other medication, and since these symptoms disappeared after the dose had been reduced, it is reasonable to attribute the ill effects to the vaccine. The focal symptoms were improved in spite of the constitutional reactions.

The above cases are presented to illustrate the toxic reactions which sometimes followed the use of comparatively small doses of vaccine.

In order to avoid such reactions, it was found necessary to reduce the percentage increase of the vaccines until these symptoms were no longer encountered. It was considered advisable to establish a procedure which would have a tendency to eliminate the above difficulties. Criteria for determining and tabulating reactions were then established. These were used as a basis for the following outline of vaccine dosage which has been adopted as a standard procedure (chart 1).

CHART I
Criteria for Determining Reactions and Suggestions for Dosage

Type of Reaction	Symptoms and Signs	Suggestion for Dosage Intravenous Method
1. Focal	Increased pain, tenderness, redness, swelling and/or stiffness of joints previously involved or involvement of joints not previously affected	A—Reduce 25% B—Reduce 75% C—Reduce 95% or omit one dose
2. Delayed Focal	Improvement lasting 2-4 days followed by symptoms of no. 1	A—Reduce 25% B—Reduce 75% C—Reduce 95% or omit one dose
3. General	General malaise, increased fatigue, lassitude, drowsiness, restlessness, chills (with or without elevation of temperature), nausea, headache, eye symptoms, vomiting, palpitation, precordial pain, premature contractions, nervousness, loss of weight, diarrhea, increased sweating, dizziness, mental depression, etc.	A—Reduce 50% B—Reduce 75% C—Reduce 75%
4. Delayed General	Improvement lasting 2-4 days followed by symptoms of no. 3	A—Reduce 50% B—Reduce 75% C—Reduce 75%
5. Both Focal and General	Both symptoms of no. 1 and no. 3	A—Reduce 50% B—Reduce 75% C—Reduce 95% or omit one dose
6. Delayed Focal and General	Improvement lasting 2-4 days followed by symptoms of no. 1 and no. 3	A—Reduce 50% B—Reduce 75% C—Reduce 75%
7. None	No apparent effect from vaccine	Increase 10%
8. Beneficial	Improvement lasting several days	Increase 10% or repeat

The following grades are applicable to all the above reactions.

A—Mild
B—Moderate
C—Severe.

According to this outline we begin with 10 to 20 organisms and increase the dose by 10 per cent for the first few doses. If the patient pro-

CHART II
The Type of Chart Employed in the Arthritis Clinic to Record the Response to Each Injection
The data recorded indicate the response to treatment obtained in Case V.

Name S.B.		Chart No. 12327													
		Address													
Date 1932		9-20	9-27	10-4	10-11	10-18	10-25	11-1	11-8	11-15	11-22	11-29	12-6	12-13	12-21
Temperature.....	98.4	98.6	98.2	98.4	98.6	98.2	98.2	98.8	98.5	98.2	98.4	98.6	98.4	98.2	98.6
Pulse.....	110	108	106	106	110	108	108	104	106	104	102	100	90	94	92
Weight.....	114	114	114	115	114	115	115	115	116	118	115	116	118	120	121
Blood Pressure.....	150-80													130-80	
Occupation.....	None	None	None	None	None	None	None	None	None	None	None	None	None	None	None
Working.....	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No
Fatigue.....	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Drowsiness.....	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Insomnia.....	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Dermatitis.....	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No
Headaches.....	+	+	+	+	+	+	+	Heavy	No	+	No	No	+	No	No
Eyes.....	Heavy	Same	Same	No	No	No	No	+	No	+	No	No	No	No	No
Dizziness.....	No	No	No	No	No	No	No	+	No	No	No	No	No	No	No
Int. Infection.....	No	No	No	No	No	No	No	+	No	No	No	No	No	No	No
Emotional.....	No	No	No	No	No	No	No	+	No	No	No	No	No	No	No
Nervousness.....	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nausea.....	No	No	No	No	No	No	No	No	No	+	No	No	No	No	No
Vomiting.....	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No
Elimination.....	1 OD	1 OD	1 OD	1 OD	1 OD	1 OD	1 OD	1 OD	1 OD	1 OD	1 OD	1 OD	1 OD	1 OD	1 OD
Palpitation.....	No	No	No	No	No	No	No	+	No	No	No	No	No	No	No
Precord. Pain.....	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No
Toes.....	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/
Metatarso-Phalangeal	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/

/ Pain; \ Tenderness; - Swelling; | Redness; ⊕ Grating; × Stiffness; R Right; L Left.

CHART II—Continued

Name S.B.	Date 1932	9-20	9-27	10-4	10-11	10-18	10-25	11-1	11-8	11-15	11-22	11-29	12-6	12-13	12-21
Ankles.....	/	/	/	/	/	/	/	X / X	X / X	X / X	X	X	X	No	No
Knees.....	/	/	/	/	/	/	/	X / X	X / X	X / X	X	X	X	No	No
Hips.....	/	/	/	/	/	/	/	X / X	X / X	X / X	X	X	X	No	No
Lumbar Spine.....	/	/	/	/	/	/	/	X / X	X / X	X / X	X	X	X	No	No
Dorsal Spine.....	/	/	/	/	/	/	/	X / X	X / X	X / X	X	X	X	No	No
Cerv. Spine.....	/	/	/	/	/	/	/	X / X	X / X	X / X	X	X	X	No	No
Temp. Mand.....	/	/	/	/	/	/	/	X / X	X / X	X / X	X	X	X	No	No
Sterno-Clavicular.....	/	/	/	/	/	/	/	X / X	X / X	X / X	X	X	X	No	No
Shoulders.....	/	/	/	/	/	/	/	X / X	X / X	X / X	X	X	X	No	No
Elbows.....	/	/	/	/	/	/	/	X / X	X / X	X / X	X	X	X	No	No
Carpal.....	/	/	/	/	/	/	/	X / X	X / X	X / X	X	X	X	No	No
Metacarpophalangeal.....	/	/	/	/	/	/	/	X / X	X / X	X / X	X	X	X	No	No
Fingers.....	/	/	/	/	/	/	/	X / X	X / X	X / X	X	X	X	No	No
Reaction.....	/	/	/	/	/	/	/	X / X	X / X	X / X	X	X	X	No	No
Vaccine.....	/	/	/	/	/	/	/	X / X	X / X	X / X	X	X	X	No	No
Medicine.....	/	/	/	/	/	/	/	X / X	X / X	X / X	X	X	X	No	No

gresses satisfactorily, no effort is made to increase the dose more rapidly. If there is improvement, the same dose is frequently maintained over a long period of time. If, after several injections have been given, the patient's condition remains stationary, that is, if there is an indefinite response, the dose is increased rapidly, e.g. from 15 to 25 per cent. If, after increasing it in this manner, a dose is found on which the patient improves, the procedure mentioned above is followed. If improvement is not obtained in this way it is best to reduce the dose to one-tenth or one-twentieth of the initial dose and proceed according to chart 1. In some cases a greater percentage of increase may be tolerated but it may often lead to a severe focal reaction, the patient may become markedly worse and it may require one or two months to repair the damage. (See Case II.) We, therefore, do not recommend an increase of over 25 per cent at any time. If a reaction occurs, the dose must be reduced according to its severity. (See chart 1.) In some cases we have observed that one or more joints have been improved, while others have become worse. In these instances, the dose is reduced until no untoward reaction is obtained in the most hypersensitive joint and the procedure outlined in chart 1 is followed.

In the recent cases the weather has been recorded on a chart with space for temperature, barometric pressure, humidity, and atmospheric conditions and our observations of the reactions have been modified by these reports. The adoption of the above measures has enabled us to obtain the maximum degree of improvement with the minimum of unfavorable reactions. The following case report (Case V) illustrates the response to treatment based on the above procedure.

CASE V

A strain of viridans with an agglutinin titer of 1:10,240 was recovered from the throat of a patient with arthritis. An initial dose of 50 organisms was given, which was followed by a favorable response. This was repeated several times and then increased on an average of 15 per cent each time. On one occasion, when the dose was increased 25 per cent (from 80 to 100 organisms), there was a definite focal reaction. The maximum dose given this patient was 100 and the average was 60 organisms. Definite improvement was obtained as shown by chart 2. At the beginning of treatment, there was a marked involvement of most of the joints of the body, whereas, after 14 weeks of treatment, there remained only swelling and stiffness in the hands and fingers. (See chart 2.) The patient had gained eight pounds in weight, the constitutional symptoms were markedly improved and she was able to carry on her household duties without difficulty. The sedimentation rate at the beginning of treatment was 65 mm. per hour. At the end of 14 weeks it was reduced to 35 mm. per hour (a drop of 30 mm.). The basal metabolic rate at the beginning of treatment was plus 16 and at the end of 14 weeks it was plus 17. This case illustrates the results obtained with the procedure outlined in this paper.

ANALYSIS OF 100 CASES

In the above series, we have used the classification adopted by the New York clinics. (See chart 3.)

CHART III

Classification of Arthritis and Allied Conditions

1. ARTHRITIS

Group 1 (Infectious)

- a. Arthritis of rheumatic fever (Synonym: Rheumatic disease)
- b. Rheumatoid arthritis (Synonyms: 1. Chronic infectious arthritis
2. Atrophic arthritis
3. Proliferative arthritis
4. Marie-Strumpell disease and Still's disease)
- c. Arthritis caused by known specific microorganism. (Named according to etiologic organism)

Group 2 (Degenerative)

- Osteoarthritis (Syn.: Hypertrophic arthritis, including Heberden's nodes and malum coxae senilis)

Group 3 (Allergic)

- Serum sickness

Group 4 (Traumatic)

- Includes occupational injuries, loose cartilages, sprains, etc. (Named according to joint involved)

Group 5 (Metabolic)

- a. Gout
- b. Scurvy
- c. Rickets
- d. Ochronosis

Group 6. Neurogenic arthropathy. (Including Charcot's joint, posthemiplegic, etc.)

Group 7 (Mixed)

- Includes any combination of the above.

Group 8 (Unclassified)

- a. Any arthritis of uncertain type.
- b. Any arthritis not included in the above.

2. ALLIED CONDITIONS

Named according to etiology, if known, and anatomical part involved.

- a. Bursitis
- b. Neuritis
- c. Myositis
- d. Fascitis
- e. Myofascitis

(Example: Bursitis, traumatic, right subdeltoid)

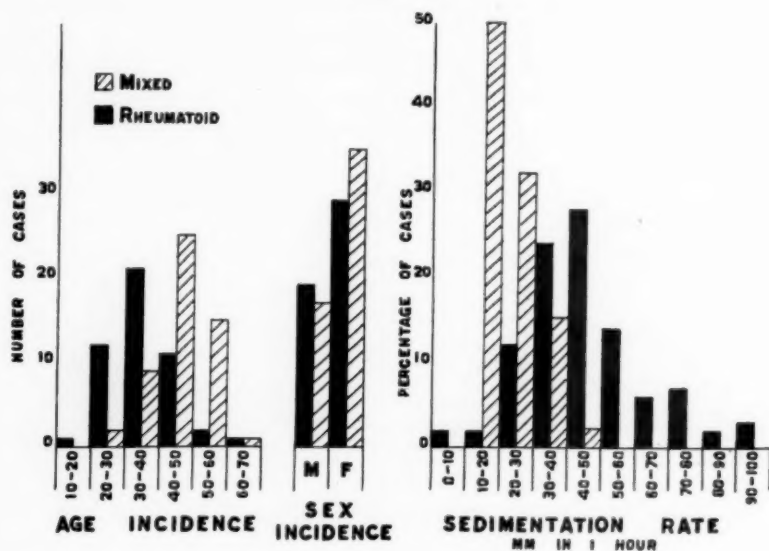
In the rheumatoid group, we have included only those cases showing the typical, bilaterally symmetrical, spindle-shaped swelling of the second phalangeal joints of the fingers. There were a large number of cases showing a polyarthritis of long duration which is frequently classed as rheumatoid arthritis, but they showed evidence of other factors and we believed that they should be placed in the mixed group. This accounts for the relatively large number of cases of mixed arthritis in this series. There were 48 of the rheumatoid type and 52 of the mixed.

Age Incidence. The rheumatoid group occurred with increasing frequency from the early part of the second decade, reaching its maximum in the middle of the third decade, whereas, the mixed group occurred with increasing frequency from the middle of the third decade, reaching its maximum in the middle of the fourth. (See chart 4.)

Sex Incidence. In our series, both types of arthritis were more frequent in females than in males. (See chart 4.)

Sedimentation Rate. The highest sedimentation rate was found in the rheumatoid group, 84 per cent having a sedimentation rate of 30 mm. or more per hour. (Westergren technic.) The mixed group gave a lower rate, 26 (50 per cent) being between 10 and 20 mm.; 16 (32.5 per cent), between 20 and 30 mm.; 8 (15.2 per cent), between 30 and 40 mm.; and 2 (2.2 per cent) above 40 mm. (See chart 4.)

CHART IV



Our findings agree with previous reports that the sedimentation rate is higher in rheumatoid arthritis and is proportional to the activity of the disease.

Blood Counts. Numerous counts were done on a large number of patients to determine the effect, if any, of the intravenous administration of vaccine on the red, white and differential blood counts. In order to determine the normal in relation to meals, time of day, etc. the patients' diets were standardized and a number of counts made each hour of the day before vaccine therapy was instituted. The same procedure was followed after the administration of vaccine and compared with the average for the same time of the day. There was no significant difference. (See chart 5.)

Duration of the Disease. The maximum was 16 years; the minimum, three months; and the average, three years.

Joints Involved. The principal difference in the findings of the two types of arthritis was in the greater frequency of involvement of the fingers, hands and mandible in the rheumatoid group. In both types the knees, ankles, wrists, hands, shoulders, feet and fingers were more frequently involved. It is also of interest to note the frequency of involvement

of the cervical and lumbar spine (see chart 6) and to note that the initial symptoms frequently occurred in the cervical spine.

CHART V
Blood Counts
Average Blood Counts Before Vaccine Therapy *

Time of Day	R.B.C.	W.B.C.	Hgb. per cent	Differential (per cent)			
				Polys.	Lymph.	Mono.	Eos.
9 a.m.	4,450,000	7,100	80	58	33	6	3
10 a.m.	4,300,000	7,000		56	34	6	4
11 a.m.	4,180,000	7,750		60	32	6	2
12 a.m.	4,700,000	7,950		58	30	9	3
1 p.m.	4,540,000	7,250		58	28	11	3
2 p.m.	4,400,000	7,400		60	31	8	1
3 p.m.	4,150,000	6,800		54	38	6	2
4 p.m.	4,310,000	6,650		52	38	7	3
5 p.m.	4,400,000	6,100		54	34	10	2

Average Blood Counts After Vaccine Therapy †

Time of Day	Interval after Vaccine	R.B.C.	W.B.C.	Hgb. per cent	Differential (per cent)			
					Polys.	Lymph.	Mono.	Eos.
10 a.m.	1 hr.	4,300,000	7,350	80	56	33	7	4
11 a.m.	2 hrs.	4,280,000	7,150	78	54	35	8	3
12 m.	3 hrs.	4,440,000	7,000	83	58	30	8	4
1 p.m.	4 hrs.	4,650,000	6,800	80	55	33	9	3
2 p.m.	5 hrs.	4,460,000	7,600	79	59	32	8	1
3 p.m.	6 hrs.	4,320,000	7,400	82	52	40	8	1
4 p.m.	7 hrs.	4,200,000	8,300	83	55	34	6	1
5 p.m.	8 hrs.	4,400,000	8,000	84	51	37	8	4
6 p.m.	9 hrs.	4,320,000	7,800	82	56	33	7	4
9 a.m.	24 hrs.	4,530,000	6,800	85	52	39	7	2
3 p.m.	30 hrs.	4,640,000	8,000	83	58	34	5	1
9 a.m.	48 hrs.	4,400,000	7,800	84	56	35	7	2
3 p.m.	54 hrs.	4,530,000	8,300	89	57	34	6	3
9 a.m.	72 hrs.	4,310,000	7,400	83	53	38	7	2
9 a.m.	90 hrs.	4,400,000	6,800	77	59	31	8	2
9 a.m.	120 hrs.	4,700,000	8,300	79	55	36	8	1

* Counts were made hourly during the daytime for four days. The figures given represent the average for each hour, based on a study of 25 patients.

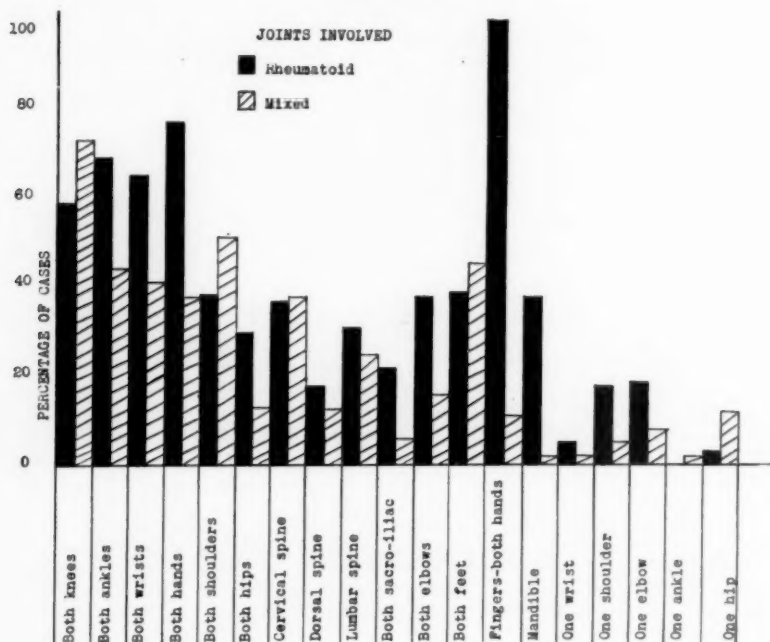
† Similar observations were made and extended over a period of five days after each dose.

Foci. No foci were removed in this group after treatment was instituted and all those mentioned below had previously had some form of treatment without apparent benefit.

There were 33 patients who had previously had teeth extracted, with improvement in six cases (18 per cent); 30 had had tonsils removed with improvement in three (10 per cent); six had had cholecystectomies with improvement in three (50 per cent); four had had gynecological operations with no improvement; four had received massage for an infected prostate

with improvement in one (25 per cent). This makes a total of 90 patients who had previously had foci removed or treated, with improvement in 18 (20 per cent).

CHART VI



An effort should be made to remove foci of infection but this alone is insufficient to effect a cure. After-treatment is necessary to obtain maximum improvement.

TREATMENT

In the rheumatoid group, the longest period of treatment was 22 months; the shortest, four months; the average, 10 months.

In the mixed group, the longest period of treatment was 20 months; the shortest, four months; the average, nine months.

The injections were usually given twice weekly. The dose was never very high in any case, the highest single dose given being 10 millions; the lowest, 10 organisms; and the average, from 500 to 2,000. Many patients did not receive more than 500 organisms at any time. No other medication was given.

RESULTS

In order to appraise the results obtained, it was necessary to establish criteria on which to base conclusions. We adopted the following: (1) reduction in pain, swelling and stiffness with increase of function; (2) lessening of any deformities; (3) improvement in constitutional symptoms;

and (4) lowering of the sedimentation rate. As previously mentioned, consideration was given to variations of the weather and most of the group were observed during both winter and summer months. An effort was made to determine the percentage of improvement, based upon the above criteria, and any patient with less than 25 per cent improvement was considered unimproved.

Of the rheumatoid group (48 cases), 39 (81.35 per cent) were improved and nine (18.65 per cent) were unimproved. Of the mixed group (52 cases), 40 (77 per cent) were improved and 12 (23 per cent) were unimproved. Of the total number of cases studied, 79 per cent were improved and 21 per cent unimproved. These results were obtained with patients who had had arthritis for a considerable time. In another series of patients with a shorter duration, we have obtained a higher percentage of improvement. Improvement was in general inversely proportional to the duration of the disease.

DISCUSSION

It became apparent from weekly observations over a period of several years, that natural remissions in rheumatoid and mixed arthritis were much less frequent than in rheumatic fever. When present, they were evanescent in character. Although this constancy of symptoms is unfortunate for the patient, it is a valuable aid in the interpretation of the effects of any type of treatment. Therefore, we chose for this study patients with rheumatoid or mixed types of chronic arthritis which had run a chronic course and was either at a standstill or was growing progressively worse. It is unwise to suggest a fixed dosage to be used in all cases. The routine procedure as outlined in chart 1 was used merely as a working basis, a starting point from which one must deviate according to individual variations. The percentage increase in dosage which may be tolerated by different patients is extremely variable. This phenomenon may be explained in part by the difference in the sensitivity of each patient and partly by the degree of specificity of the vaccine used. The persistence of foci of infection will tend to maintain a degree of hypersensitiveness which interferes with the progress of vaccine therapy and retards improvement. In cases presenting an extreme sensitivity to the autogenous vaccine and in which it is impossible to obtain improvement, a "hidden" focus of infection should be sought.

In the beginning, we attempted to increase the dose as rapidly as advocated by other workers but, as previously mentioned, this produced unfavorable reactions. We believe that better results are obtained by maintaining a small dose over a long period of time.

Since we began this work, the proportion of patients who have been given vaccines intravenously has steadily increased. More than 300 patients with chronic arthritis (rheumatoid and mixed types) of all grades of severity have been treated by the above methods. Although improvement

has not occurred in all, the results have been far more satisfactory and encouraging than with other methods of treatment which we have used.

SUMMARY AND CONCLUSIONS

1. Patients with rheumatoid or mixed types of chronic arthritis were treated by the intravenous administration of vaccines under suitably controlled conditions. The antigens used consisted of phenolized, unheated, autogenous strains of streptococci having high agglutinin titers with the patients' own serums.

2. Repeated small doses of vaccine given intravenously tend to desensitize the patient.

3. A plan for the general administration of such vaccines has been outlined. This can be followed in ambulatory patients with little danger of causing unfavorable reactions.

4. We have been unable to increase the dosage as rapidly as other authors have advocated.

5. We have purposely avoided the term "cure." We believe it rash to make such a claim until patients have been followed over a prolonged period.

6. Improvement has been obtained in 79 per cent of the cases.

7. We believe these results warrant further studies along similar lines.

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XANTHOMA ACCOMPANIED BY HYPERCHOLESTEROLEMIA, OCCURRING IN AN OTHERWISE NORMAL INDIVIDUAL, AND IN AN INDIVIDUAL WITH ACROMEGALY AND DIABETES *

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THE STUDY of fat metabolism, and of the rôle it plays in the animal economy, has been diligently pursued by many investigators, especially in recent years. As a result of this impetus, lipid metabolism, and particularly cholesterol utilization, is being investigated constantly in a great variety of pathologic conditions.

Alteration in the normal utilization of the lipid substances is found ordinarily as a complicating condition in some more profound disease process, although it may occur spontaneously. However, regardless of the etiology of such disturbance, the accumulation of the lipids in the organism frequently acts as a morbid factor, the effects of which may ramify to distant parts of the body.

Disseminated xanthomatosis, exclusive of xanthoma palpebrarum is an unusual manifestation of disturbed fat metabolism resulting from an infiltration of lipid substances into the skin and other tissues. It may occur either as a complication, usually of diabetes mellitus, or as an idiopathic condition. It is a rare disease as is evidenced by the fact that of 18,400 consecutive medical admissions to The Johns Hopkins Hospital, xanthomas were found in only 3 instances.¹ It should be added, however, that treatment of the disease does not usually require hospitalization. Bloch² collected and analyzed 96 cases of the disease and these represent all of the idiopathic type appearing in the literature to 1931, in which blood cholesterol determinations have been made. Wile³ has recorded all of the known instances of familial xanthoma involving 14 families and including 42 patients.

Xanthoma diabeticorum is also rare. In 1924, Major⁴ reported 3 cases and reviewed 71 others previously appearing in the literature. We have appended a chronologically arranged list of the 23 cases reported since that time,⁵ bringing the total number of known diabetic xanthomas to 97.

The concomitant occurrence of acromegaly and diabetes mellitus has been well established,^{6, 7, 8} although disseminated xanthomatosis complicating such a condition has been recorded in but two instances.^{9, 10} In both of these, as in the second case here reported, the acromegaly had preceded by some time the onset of the diabetes.

While xanthomatous tumors have been known to occur in the absence of elevated blood cholesterol values,^{11, 12, 13, 14} and indeed in the presence of

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values as low as 44 mg. per cent,¹⁵ hyperlipoidemia and hypercholesterolemia are decidedly the rule. Ingram¹⁶ observed low values for cholesterol in seven out of 58 cases studied, but Wile, Eckstein and Curtis¹² and also Rowland¹⁷ have suggested that the xanthomatous lesions make their appearance only in the presence of an hyperlipoidemia; low lipoid values subsequently may be obtained although the tumor nodules remain unchanged. They believe, "that a disordered fat metabolism in which cholesterol undoubtedly plays a part as a constituent of the body lipoids is responsible for xanthoma." Bloch² and Schaaf¹¹ have presented evidence showing that disturbance in the normal proportionate relationship between the various lipoids of the blood (cholesterol, cholesterol esters, phosphatides, fatty acids, neutral fats and soaps) is the determining factor for their deposition in the blood and tissues. "All the lipoid constituents with the exception of soaps are insoluble in water. Consequently they do not exist in the serum in a dissolved form, but in that of a finely dispersed stable emulsion. The normal proportion of all the lipoid constituents must be maintained in the blood, in order that they should fulfill their proper function. The proportions, which normally exist between the lipid constituents of the blood and between these substances and the albumin of the serum, constitute the best index of the stability of this complex emulsion. If the proportion is changed considerably in any direction, i.e., if the amount of any, or several, of these constituents is altered, the result, according to the laws of colloidal theory, is a disturbance in the stable aqueous, lipid emulsion, the blood serum. A disproportion of this kind leads to a coarsening of the lipid particles in the emulsion, and in the higher degrees to separation and finally precipitation of individual constituents in the tissues—in a word, to xanthomatous lesions." Rowland,¹⁷ Leites,¹⁸ Weber,¹⁹ and Jaffe²⁰ all conclude that the production of xanthoma results not merely from a passive "supersaturation" precipitation, but rather from an active process in which the reticulo-endothelial system plays an essential rôle. The absorptive and secretive power of this system for cholesterol has been shown to vary with changes in its physiochemical state¹⁸ so that, "All the varied xanthoma manifestations can be brought back to a single pathologic principle; the reticulo-endothelial system is infiltrated by certain substances."¹⁷

The typical xanthoma cell is a reticulo-endothelial cell infiltrated with lipoids. The lipoid disturbance is apparently primary,^{21, 22, 23} a fact which may explain why xanthomatosis is most commonly associated with diseases such as diabetes, nephritis, and obstructive jaundice in which there is likely to be an increased blood cholesterol.^{20, 21, 24, 25, 26} Deposit in the reticulo-endothelial tissues is secondary. However, as Weidman²⁷ points out, "Some factor in addition to the mere presence of hypercholesterolemia and young connective tissue cells is necessary to the development of xanthoma tuberosum." Other contributing factors in the formation of these unusual nodules mentioned by various writers and of interest in connection with the cases here described include the duration of the blood condition, trauma,²⁸ local vascular supply^{17, 22} and local or systemic infection.^{17, 28}

CASE I

E. W., an American, male, carpenter, aged 27, entered the clinic September 19, 1931, complaining chiefly of a papular eruption on the palmar surfaces of his hands as well as other parts of his body. His only other complaint was the infrequent occurrence of abdominal distention and gaseous eructations after meals. His family history was unimportant and lacked any example of a dermatosis similar to his own. His personal anamnesis included measles and whooping cough in childhood, appendicitis (operated) at the age of 17 years, and a Neisserian infection of six to seven weeks' duration at the age of 18 years. His present troubles began about two years



FIG. 1. Case I. Lesions about the elbows as they appeared in November 1931.

prior to entry with slight pain on kneeling and the simultaneous appearance of papular, grouped lesions over both knees. Within the next six months similar nodules appeared on the palmar surface of both hands and about the elbows. Within the last six months, papules have appeared over the buttocks and along the entire posterior surface of the thighs. The lesions are painless although discomfort results from such irritation as pressure. The abdominal distress after meals had been noted for several years, was intermittent in character, and occurred usually after eating highly seasoned or "greasy" foods. His diet consisted essentially of meats and starches; few green vegetables were included. It is particularly interesting that he has never liked or eaten butter or other fats. Coffee and tea were rarely used; he customarily drank five or six pints of home-brewed beer daily.

Physical examination revealed a well developed man weighing 72 kg. (158.4 pounds) and measuring in height 162.5 cm. (5 feet, 5 inches). Abnormal findings were confined to the skin, which displayed firm, papular and nodular, yellow to saffron-colored lesions distributed over the extensor surfaces of both elbows, both knees, the buttocks and the posterior aspects of both thighs, in the palms of both hands and on the fingers (figures 1 and 2). These lesions varied in diameter from 2 mm. to 1½ cm., being smallest on the thighs and palms of the hands and largest about the elbows and knees.



FIG. 2. Case I. Lesions in the palms of the hands as they appeared in November 1931.

Laboratory findings: The urine had a specific gravity of 1.019; sugar and albumin were absent. The sediment contained only the normal constituents. The fasting blood sugar was 110 mg. per cent. A sugar tolerance curve showed the following levels after the ingestion of 100 grams of glucose: Fasting, 105 mg. per cent; one-half hour, 122 mg. per cent; one hour, 115 mg. per cent; two hours, 98 mg. per cent. The fasting (14 hours) blood plasma cholesterol was 1075 mg. per cent (average of two determinations on a single specimen). The carbon dioxide combining power of the plasma was 53.1 volumes per cent. The blood plasma chlorides were 556 mg. per cent; the non-protein-nitrogen 38.9 mg. per cent; the urea nitrogen 17.1 mg. per cent. Cholecystography by the oral method revealed a normally functioning gall-bladder. The rose bengal test for liver function was normal, showing 55 per cent excretion of the dye in the first eight minutes, and an additional 33 per cent in the second eight minute period. Results of the blood count were: red blood cells 5,450,000; hemoglobin (Sahli) 98 per cent; white blood cells 7,650; polymorphonuclear neutrophils 71 per cent; eosinophiles 3 per cent; basophiles 1 per cent; small lymphocytes 18 per cent; large lymphocytes 6 per cent. The basal metabolic rate was minus 6.1 per cent. Roentgen-rays of the skull, chest, feet and legs showed no evidence of bony change, nor did the vessels of the extremities appear sclerosed.

Course: This is summarized in chart 1. On an ordinary diet from September

CHART I
Summary of Findings in E.W. (Case I)

Date	Weight in lbs.	Diet				Blood cholesterol in mg. per cent			Medication	Remarks
		CHO	Prot.	Fat	Cal.	Whole	Plasma	Esterin Plasma		
9-21-31	158.4						1075		None	Glucose tolerance curve low
10-20-31	158.0		General		2490		742		"	Blood chemistry normal (see text).
11- 4-31	—	350	70	90			605		"	Low cholesterol diet. B.M.R. 6.1% minus.
11-10-31	—	"	"	"	"		464		"	
12- 3-31	156.5	"	"	"	"		757		"	Digestive symptoms worse.
12-29-31	—	"	"	"	"		476		"	4 egg yolks added to daily diet.
1-16-32	—	"	81	110	2714		445		"	Has had mild bronchitis.
1-23-32	—	"	"	"	"	375	510	219	"	Egg yolks discontinued.
2- 1-32	157.0	"	"	"	"		432		"	
3- 5-32	—	"	70	90	2490		568		Insulin U-40 daily	B.M.R. 3.0% minus.
3- 9-32	—	"	"	"	"		610		Insulin U-60 daily	
3-12-32	—	"	"	"	"		472		"	
3-16-32	—	"	"	"	"	298	456		"	
3-27-32	—	"	"	"	"		470		"	
4- 5-32	—	"	"	"	"	320	406		"	
4-19-32	155.0	"	"	"	"	309	402		"	
5-10-32	155.0	"	"	"	"		455		"	B.M.R. 2.1% minus.
5-17-32	153.6	"	"	"	"		500		Insulin stopped	Fasting blood sugar 0.81%.
7- 5-32	148.5	"	"	"	"				Thyroid gr. ii daily	
8-27-32	151.0	"	"	"	"	287	357		Thyroid gr. v daily	
9-19-32	151.5	"	"	"	"	439	629	321	"	States has dieted carefully. B.M.R. 2.1% minus.

19, 1931 to October 22, 1931, the patient's blood plasma cholesterol fell from 1075 mg. per cent to 742 mg. per cent. On the latter date his dietary regime was changed to a high carbohydrate, low fat, low cholesterol diet (CHO 350 gm., P 70 gm., and F 90 gm.). This was continued until January 16, 1932, at which time a definite softening of all of the skin lesions could be noted. The blood plasma cholesterol had receded to 445 mg. per cent. The gastrointestinal symptoms remained unchanged. Four egg yolks daily were then added to the diet. Two weeks later, the plasma cholesterol was 430 mg. per cent. Because of the obvious lack of effect of the additional egg yolks on the cholesterol content of the blood and because of the patient's dislike for eggs, the latter were discontinued. Pending an opportunity to hospitalize the patient no further changes were made in his regimen until March 5, 1932. He entered the University Hospital on this date. From then until May 10, 1932, 60 units of insulin were administered daily. During this period the blood plasma cholesterol varied from 568 mg. per cent to 402 mg. per cent. Thyroid substance (Armour's desiccated) was started early in May, and the dose gradually increased until in three



FIG. 3. Case I. Lesions about the elbows as they appeared in January 1933. Very marked reduction in number and size of xanthoma.

weeks the patient was receiving 5 grains daily. This dosage has been continued to date (October 15, 1932) with but four pounds loss of weight. No change in pulse rate and no elevation in the metabolic rate have occurred—the most recent determination being 2.1 per cent minus on September 19, 1932. The blood plasma cholesterol has fluctuated from 500 mg. per cent at the beginning of the period through a low point of 357 mg. per cent in July to a present (October 15, 1932) value of 629 mg. per cent. From the beginning of the administration of the high carbohydrate, low fat diet there has been a gradual but definite recession of the lesions, most marked in the period of thyroid administration. All of the lesions are softer and less rounded.

About the elbows especially, recession is associated with a change of the nodular condition to one of scale or crust formation. When the crusts drop or are pulled away, they expose an area of approximately normal skin, surrounded by a very faint erythematous zone. Many of the lesions in the hands and about the elbows have entirely disappeared. (Figures 3, 4, and 5.)



FIG. 4. Case I. Taken in January 1933. Lesions about the elbows are fewer in number and much softer.

CASE II

W. A., a 33 year old single negress first reported to the clinic October 5, 1928, complaining of generalized weakness, amenorrhea and blurring of vision. A de-

creasing and irregular menstrual cycle—her earliest symptom of ill health—made its appearance at the age of 24 years. One year later complete amenorrhea supervened and has persisted. At the age of 30 years, she noticed a disturbance of vision and, when fitted for glasses, found it "difficult to get a sufficiently wide frame." She



FIG. 5. Case I. Taken in January 1933. Xanthoma have disappeared from palms of hands.

began to require progressively larger gloves and shoes. Three months before coming to the clinic, aet. 33, polyphagia and polydipsia (but not polyuria) made their appearance. She became increasingly irritable, suffered from severe frontal headaches, nocthidrosis, and generalized asthenia.

Physical examination (see figure 6) at that time revealed an individual whose appearance was typical of acromegaly. The brow was low and wide with wrinkled folds of skin and prominent frontal bossae. The eyes were widely separated with puffy upper lids, widened palpebral apertures and a suggestion of exophthalmos. There was a bilateral external strabismus. The pupils were regular, round and dilated. The right responded to light but not to accommodation, the left to neither light nor accommodation. Vision in the right eye was 20/70, using a plus two lens. Light perception was questionable in the left eye. Fundal examination revealed a well advanced optic atrophy on the left side. There was no choking of either disc. Perception in the left eye was too poor for perimetric field determinations but the right eye showed complete blindness over the temporal half of the fundus. The nose and lips were wide and thick; the malar prominences slightly flattened. Marked prognathism was apparent. The incisor teeth were widely spaced; the tongue was huge, wide and long. Hair distribution was normal. The thyroid gland was normal. Heart and lungs were normal but the bony thorax was enlarged. Blood pressure was 110 systolic and 85 diastolic. No abnormalities were noted in the abdomen. The hands and feet were broad and long. The fingers were flat and wide without the normal taper. (Figure 9.) The toes were similarly shaped. There was slight cervico-dorsal kyphosis. The skin was swarthy with freckles, thick but smooth.

Laboratory procedures revealed a negative Wassermann, a basal metabolic rate of 4.1 per cent minus, glycosuria and a definitely lowered sugar tolerance. (See chart 2.) The blood count was normal. Roentgen-ray of the skull evidenced "a marked enlargement of the sella turcica with thinning of the anterior and posterior clinoid processes and depression of the floor." (See figure 6.) Roentgen-rays of the hands and feet showed "some clubbing of the distal phalanges but practically no enlarge-



FIG. 6. Case II. Photograph and roentgen-ray taken in October 1928, nine years after the first symptoms of pituitary disease were noted. Low brow with wrinkled skin folds; wide separation of eyes; external strabismus; prognathism. Note the large sella turcica with erosion of anterior and posterior clinoid processes. Roentgen-ray findings in 1932 are essentially like those shown here.

ment of the bones from sub-periosteal bone. There is an exostosis in the same place on both great toes. There are defects in the bone of the terminal phalanges of the thumb at corresponding points, and of the left fifth digit about the proximal interphalangeal joint." (Dr. Stone.)

At this time, a diagnosis was made by Dr. Hans Lissner of pituitary tumor resulting in acromegaly with amenorrhea, possibly hypophyseal diabetes and optic atrophy.

Course: A transphenoidal hypophysectomy was done October 23, 1928, by Dr. Fleming, from which recovery was uneventful. Microscopic examination of the excised tumor showed it to be a chromophilic adenoma. Within the two weeks immediately following operation, four roentgen-ray treatments—each representing one-half of a skin erythema dose—were given to the hypophyseal region. Subsequent to operation, headache and nocthidrosis promptly disappeared. There has been steady improvement in eyesight, as was noted by comparing the perimetric fields taken just prior to operation, in October 1928, with those taken in May 1932. Visual acuity of the right eye has improved from 20/70 to 20/40, and of the left eye from almost complete blindness to 20/120.

The persistence of glycosuria and hyperglycemia, despite steady improvement in other symptoms usually ascribed to pressure about the hypophyseal region, finally necessitated a diagnosis of true diabetes mellitus. Quantitative care of that condition was begun in May 1929. Management of the diabetes, unfortunately complicated by a pulmonary abscess, necessitating hospitalization for five weeks in May and June 1929, has been difficult although supposedly the patient has been on only slightly more than a basal diet throughout her illness. Abstracts from her record, shown in chart 2, give some suggestion of the difficulties encountered.

CHART II
Summary of Findings in W.A. (Case II)

Date	Wt. in lbs.	Daily Diet				Blood sugar tolerance curve in mg. per cent				Four period urine				Blood cholesterol			B.M.R.	Remarks
		CHO gm.	Prot. gm.	Fat gm.	Cal.	Insulin Daily Units	Fasting	1 hour	1 1/2 hours	1st	2d	3d	4th	Whole mg. %	Plasma mg. %	Hrs. after food		
10-6-28	149.5	Ordinary household				0	116	206	217	206	Green	Olive	Olive				-4.1%	
11-6-28		General Hospital				0	93	207	256	210	Blue	Green	Yellow				-1.5%	13th day after hypophysectomy.
2-9-29		Ordinary household				0	336	523	530	555	Orange	Orange	Orange					Respiratory infection.
5-14-29	135.5	General Hospital				0	268			Single specimen								Entered Hospital for lung abscess.
6-14-29		100	90	110	1750	40	70	185	287	200	Orange	Orange	Orange				-15.9%	Convalescing from lung abscess.
8-14-29	125.0	"	"	"	"	?				Orange	Orange	Orange	Orange					Has not dieted carefully or used insulin regularly. First visit to Diabetic Clinic.
9-4-29	128.3	100	80	80	1440	30				Blue	Yellow	Olive	Blue				+0.9%	
9-20-29	130.2	"	"	"	"	35	333	551	544	Red	Olive	Red	Yellow					
10-1-29	132.4	"	"	"	"	40				Blue	Green	Green	Blue					
10-14-29	135.0	"	"	"	"	50	189	333	444	284							-2.1%	
10-23-29		"	"	"	"	52				Blue	Green	Blue	Blue					
12-4-29	138.2	"	"	"	"	68	472			Red	Red	Olive	Yellow					Had 4 x-ray tfs to hypophysis Nov. 1-8 each 1/2 SED. Weighing diet carefully. Some headache since beginning x-ray.
3-21-30	131.6	"	"	"	"	0	333	-2 1/2	hours	p.c.	Single specimen						-21.9%	Acetone ++ Diacetic acid + No insulin since Jan. 1, 1930. Has not attended Clinic in that time.
4-11-30	133.0	100	60	100	1540	50				Blue	Green	Blue	Blue					
12-8-31	142.6	130	70	90	1610	50				Green	Green	Olive	Green					Has been fairly well controlled on diet noted 4-11-30 and insulin ranging from 40-50 U daily; effects of high CHO diet to be tried.
4-12-32	146.4	"	"	"	"	55	384	-2 1/2	hours	Green	Green	Green	Green		1150	2 1/2		Blood plasma milky and thick.
7-19-32		"	"	"	"	55	377	-1 1/2	hours	Olive	Olive	Olive	Olive		893	1 1/2		Xanthoma appeared 5 weeks ago.
7-26-32	145.0	200	75	40	1460	60				Orange	Green	Blue	Blue					X-rays of skull negative to xanthomatous changes.
8-30-32		"	"	"	"	60				Blue	Blue	Blue	Blue	555	725	2	-1.3%	
9-20-32	144.0	"	"	"	"	70	307	-1 1/2	hours	Green	Green	Green	Green					Xanthoma condition improved.

From about January 1, 1930, to March 21, 1930, the patient did not follow the prescribed regime. She was admitted to the hospital on the latter date in coma. After relieving the acidosis, a basal metabolic rate of 21.9 per cent minus was obtained. Daily administration of one grain of desiccated thyroid substance (Armour's) was continued throughout the ensuing year with return of the metabolic rate to approximately normal.

From the time the patient was placed on a diabetic regime in May 1929, to October 15, 1932, her tolerance for carbohydrate has increased only about 25 gm. daily. Traces to appreciable amounts of sugar have been found in the urine from



FIG. 7. Case II. Xanthomatous lesions about the elbows as they appeared in July 1932.

time to time. While the fasting blood sugar has at times been within normal range, it is usually elevated, and all post-prandial determinations have revealed a marked hyperglycemia. In view of these facts, effort was made in April 1932, to determine the state of the blood lipoids through blood cholesterol determinations. Blood withdrawn three hours after the morning meal April 12, 1932, showed a *glucose content of 384 mg. per cent and total plasma cholesterol 1150 mg. per cent.* The plasma was very thick and milky. For four months prior to this determination, the patient had been taking a moderately high carbohydrate diet (CHO 130, P 70, F 90, Cal 1610), upon which she was allowed to remain. About June 1, 1932, discrete yellowish to saffron colored nodules of from 2 mm. to 15 mm. in diameter began to make their appearance over the entire trunk and extremities. (See figures 7, 8, 9.) These were most numerous and tended to coalesce in the palms of the hands, at the elbows and about the knees. On July 19, 1932, her postcibal ($1\frac{1}{2}$ hour) blood sugar was 377 mg. per cent and the plasma cholesterol 893 mg. per cent. In an effort to improve the xanthomatous condition, which had grown steadily worse, a still higher carbohydrate



FIG. 8. Case II. Xanthomatous lesions about the knees as they appeared in July 1932.



FIG. 9. Case II. Xanthomatous lesions on dorsum of hands as they appeared in July 1932. Photographs indicate the most marked localizations of the nodules. Isolated tumefactions were scattered over the trunk, arms and thighs similar to those appearing on the right wrist in this photograph. Note the flat, wide fingers without the normal taper.

and extremely low fat, low cholesterol diet (CHO 200, P 75, F 40, Cal 1460) with appropriate insulin dosage was prescribed. At the present time (October 15, 1932), the blood plasma cholesterol has been further lowered to 725 mg. per cent; some of the lesions on the thighs have disappeared, leaving behind them pigmented scars.



FIG. 10. Case II. Xanthoma about elbows have almost disappeared and have been replaced by small pigmented scars; January 1933.

The remaining lesions have decreased in size and are more flattened in appearance. Those in the palms have ceased to cause discomfort when using the hands. (Figures 10, 11, 12.)

DISCUSSION

In the first of the two cases here reported, the fact that the xanthoma (and probably the hypercholesterolemia) had been present for at least two years may be responsible for the slowness in involution of the cutaneous lesions, as well as the difficulty in maintaining lowered blood cholesterol values. It is reasonable to suppose that Case II with pituitary disease of at least nine years' duration, and later profound disturbances in carbohydrate metabolism, evidenced alterations in blood fat long before cutaneous phenomena appeared; at least, the highest recorded cholesterol was noted two months prior to their onset.

Local trauma, consequent upon riding horseback and driving a car may



FIG. 11. Case II. Pigmented areas are the only residual evidence of the xanthomatous lesions about the knees; January 1933.



FIG. 12. Case II. Small pigmented scars indicate location of previous xanthoma; January 1933.

have predetermined the eruption of many nodules along the thighs and over the buttocks in the non-diabetic case presented. It cannot possibly account for the location of the other lesions, nor do the lesions of the diabetic patient with acromegaly suggest trauma as a factor in their distribution.

It is difficult to link the onset of cutaneous nodules with infection, local or general, in Case II, for, although she had several minor respiratory infections in the spring of 1932, none occurred within five weeks prior to the appearance of the skin tumors.

The internal secretions may play a part in xanthomatosis. Rony and Mortimer,²⁹ however, have failed to find any effect upon artificially produced lipemia in dogs as a result of the administration of the following substances: insulin, pituitrin, suprarenalin, thyroid substance, parathormone, secretin, cholecystokinin, bile salts. Their work involved short experimental periods as well as a hyperlipemia independent of endogenous disease, a factor which undoubtedly plays a rôle in the lipid disturbances associated with pathologic states. In contrast to their findings, the weight of clinical evidence suggests positive effects from some of these substances under certain conditions. It has been shown repeatedly that variation in the activity of the thyroid gland will materially alter cholesterol metabolism.^{26, 30, 31, 32, 33, 34, 35, 36, 37} Low blood cholesterol values usually supervene when an excess of thyroid is available, and high values when a deficiency exists. Storage of cholesterol in the reticulo-endothelial cells is decreased by thyroid administration.³⁷ The iodine number of the plasma fatty acids is elevated in hyperthyroidism.³³ Improvement but not total disappearance of lesions has been noted in hypothyroidism with xanthomatosis following the administration of thyroid substance together with a fat free diet.³⁸ Favorable results in other non-diabetic xanthoma following the use of thyroid extract have also been reported.^{39, 40}

In our non-diabetic patient with xanthoma, the effects of thyroid administration have been only suggestive although the cutaneous manifestations have involuted more rapidly and steadily than under any other form of treatment. The diet, amply adequate for the work performed, has been kept constant for the past eight months, thus eliminating exogenous factors. The acromegalic individual had very moderate doses of dessicated thyroid substance (1 gr. Armour's daily) for approximately one year following the low basal metabolic test in March 1930. No positive association between the xanthomata and the activity of her thyroid gland has been observable.

Although Chamberlain⁴¹ found no changes in blood plasma cholesterol following the administration of pituitary extract and although storage of cholesterol by the reticulo-endothelial system is not altered (histologic evidence) by "solution of pituitary gland,"³⁷ Moehlig and Ainslee⁴⁰ have shown the existence of a definite relationship between abnormalities of the pituitary gland itself and fat metabolism. Furthermore Ralli⁹ calls at-

tention to the decreased carbohydrate tolerance which many acromegalic patients exhibit, as well as to the incidence of true diabetes mellitus and the associated alteration in fat metabolism, occurring with acromegaly. Both Muller²⁶ and Franchini⁴³ have reported an increased excretion of cholesterol in the feces in acromegaly.

Apparently then it must be assumed from the work of various investigators that retention of the lipoid substances usually is associated with increased pituitary activity. Furthermore the chronological order of events in our Case II makes it reasonable to suppose that the primary disturbance in metabolism is to be found in the pituitary gland. The secondary manifestation, namely, true diabetes mellitus, as attested by the repeatedly high blood sugar tolerance curves, even after relief of all pressure symptoms in the region of the hypophysis, appeared much later. Lipemia and finally xanthomatosis accompanied the hyperglycemia.

Insulin influences fat metabolism through the close association of the latter with carbohydrate utilization in the body. Thus it has been shown that artificial hyperlipemia in depancreatized dogs disappears more rapidly when insulin is administered.²⁹ Also it has been suggested^{44, 45, 46} that insulin inhibits gluconeogenesis from fat, while Rony and Ching⁴⁷ have demonstrated that alimentary lipemia may be prevented by feeding carbohydrate with the fat, or by giving insulin. These latter workers conclude that the passage of sugar into the blood facilitates the passage of fat, and this has been confirmed by showing that insulin has a definite influence upon the fixation of cholesterol in the tissues.^{37, 48} However, investigations dealing with the effects of insulin on blood cholesterol have produced contradictory results, for certain workers^{41, 49} have found a reduction of an increased, but not of a normal blood cholesterol level subsequent to the administration of insulin. Also clinically, rapid reduction and disappearance of xanthomatous lesions and of hyperlipemia have been observed to follow the exhibition of insulin in the diabetic form of xanthomatous disease,^{4, 50, 51, 52} whereas in non-diabetic forms, even in the presence of hyperlipemia, insulin seems valueless.^{14, 16, 38}

In the case of non-diabetic xanthoma discussed in this paper, insulin exerted no apparent beneficial effect although the experimental period of four weeks may have been too short to warrant definite conclusions. On the other hand, the dosage of insulin used was as high as was compatible with the welfare of the individual. Moreover, no abnormality of carbohydrate metabolism is patent in this case. Abnormal carbohydrate metabolism apparently results in changes in fat utilization; the converse is not necessarily true. Steady clinical improvement of the xanthomatous nodules as well as the hypercholesterolemia has followed the use of insulin in the second case recorded, but further observations are necessary to bespeak any permanent relief from the therapy instituted. However, Rowland²¹ regards the prognosis of xanthoma diabeticorum poor as to the permanent disappearance of the cutaneous manifestations and unfavorable as to life expectancy.

Mattick and Reinhard⁵³ have shown that patients receiving roentgen-ray or radium radiation of cancerous lesions develop low blood cholesterol values. Healing of the cholesterol bone condition in the Schuller-Christian syndrome by roentgen-ray therapy but inability to prevent the appearance of new lesions has been noted.^{17, 28}

The diabetic acromegalic mentioned in this report received two series of roentgen-ray treatments to the hypophyseal region, which may have delayed the onset of xanthomatosis. At least the time interval between the onset of the acromegaly and the development of the cutaneous nodules was much longer than in the cases of Ralli and of Noothoven.¹⁰

Diet in non-diabetic xanthoma, and diet with insulin in the diabetic type probably offers the best therapeutic procedure at our disposal, although Rowland²¹ suggests that such treatment concerns itself with the hypercholesterolemia, rather than with the causative factor of generalized fat disturbance. Muller²⁶ has reported a temporary postprandial increase in the blood cholesterol of both carnivorous and omnivorous animals but notes that "a permanent increase does not depend upon food itself." Furthermore, Hunt⁵⁴ and Blix⁵⁵ found no influence upon the blood cholesterol values of controlled diabetic patients subsequent to the feeding of foods with a high cholesterol content. Probably the endogenous metabolism of cholesterol in the main is independent of the exogenous supply. But this apparently holds true only within certain limits for other workers have been able to lower or raise blood cholesterol values in man and in animals by sufficiently prolonged low or high fat diets.^{56, 57, 58, 59} A statistical report from Joslin's clinic⁶⁰ suggests that the average blood plasma cholesterol is lower than in clinics where high fat diets are allowed. From the clinical viewpoint, low caloric diets have proved necessary to bring about an involution of cutaneous xanthomata and a reduction of the hyperlipemia.^{3, 12, 50, 61} Wile, Eckstein and Curtis¹² have succinctly remarked that "the best treatment for this affection in the presence or absence of glycosuria would seem to be a reduction diet, treating the condition as one would obesity."

In both cases here recorded low fat, low cholesterol diets have been prescribed. In Case I, the calories are ample for light work. The basal metabolism remains normal regardless of the ingestion of five grains of dessicated thyroid (Armour's) substance daily. The xanthomatous nodules are gradually but steadily disappearing (figures 3, 4, 5), despite the fluctuating blood cholesterol. Such a course is in apparent contrast to other cases in which low caloric equivalents, with or without thyroid extract, were necessary to cause involution. The diabetic patient with xanthoma has been placed on a diet of approximately a basal maintenance caloric requirement. Clinical improvement is obvious in the xanthomatous lesions (figures 10, 11, 12), but carbohydrate metabolism has not yet approached normal levels. It has been impossible to hospitalize her recently and the suspicion

remains that she either consciously or unconsciously ingests more food than prescribed.

The unusually high initial cholesterol values found in these patients (1075 and 1150 mg. per cent, respectively) are of especial interest and for that reason were in each case repeatedly checked. The method of total cholesterol estimation was that of Bloor,⁶² and for free cholesterol that of Bloor and Knudson.⁶³ As far as we have searched the literature, only two instances of higher values are found. Engman's⁵⁰ patient with diabetic xanthoma had a blood plasma cholesterol of 1,800 mg. per cent (normal value by the method used, 300 mg. per cent). Bloor⁶⁴ records a case of diabetic lipemia without xanthoma in which the blood plasma cholesterol was 1,370 mg. per cent (estimation by Bloor's original method, 1916). Brown and Howard¹ found a value for serum cholesterol of 1,000 mg. per cent in a non-diabetic patient with disseminated xanthoma (method not mentioned). In Rowland's^{17, 21} cases the highest figures for plasma cholesterol in xanthomatosis were just under 600 mg. per cent.

In the two patients here described the low whole blood cholesterol determinations, as contrasted with those for plasma cholesterol, show the tendency of the red corpuscles to maintain a constant cholesterol content in spite of marked changes in the plasma. This is nicely exemplified in Case I, in which roughly calculated values for cholesterol in the corpuscles have been well within the normal range, despite the high plasma cholesterol. In this connection Mayer and Schaeffer⁶⁵ have suggested that the corpuscles of the blood behave more or less as tissue cells, that is, have a fairly constant composition in contrast to the blood plasma. It is evident, however, that this ability of the corpuscles to maintain a normal cholesterol content is not complete, as the red cells in an "emergency" can also be "loaded" with fat and phospholipid.^{26, 64} Such storage of lipoids in the corpuscles apparently exists in our second patient.

Because a disturbance in the relative proportions of the individual blood lipid bodies has been suggested as a causative factor in xanthomatosis, attempt was made to follow the ester fraction of the blood plasma cholesterol in the first case here described. On two occasions, this was increased in direct proportion to the elevation of the total cholesterol; no conclusions are possible without more frequent analyses.

SUMMARY

1. The incidence of xanthomatosis (excepting the Schuller-Christian syndrome and Niemann Pick's disease) is noted as recorded in the literature.
2. Findings in one case of idiopathic disseminated xanthomatosis, and in one case of acromegaly with xanthoma diabeticorum, are recorded.
3. In the non-diabetic individual, moderately restricted diet and thyroid gland administration have been attended by a partial involution of the xanthomatous lesions. High cholesterol feeding for a short period (two weeks) did not affect the blood cholesterol level. Insulin administration had no obvious effect upon either the blood or cutaneous disturbance.

4. In the acromegalic patient with xanthoma diabeticorum, administration of a high carbohydrate, low fat and low caloric diet with insulin, has been accompanied by some lowering of the hypercholesterolemia and a diminution in the number and size of the skin nodules.

5. Features of especial interest are noted: (a) the rarity of the condition exhibited in the second patient—association of acromegaly, diabetes mellitus and xanthoma diabeticorum; (b) the excessively high blood cholesterol values in both cases; (c) the low cholesterol content of the blood corpuscles despite very high plasma values.

6. Some factors concerned in cholesterol metabolism and in the production of xanthoma are discussed with particular reference to the cases reported.

CONCLUSIONS

It is well nigh impossible to make sweeping deductions concerning a condition, the incidence of which is so rare as to preclude observations in a large series of cases. However, the facts here presented seem to warrant the following comments:

1. Disturbed carbohydrate utilization is not a necessary antecedent to altered fat metabolism.

2. Insulin is without value in the treatment of non-diabetic xanthoma, but is important in the management of the diabetic type.

3. Dessicated thyroid substance apparently has a favorable influence upon involution of non-diabetic xanthoma.

4. Diets with a reduced fat component and of low caloric equivalents afford the quickest method of causing involution in diabetic and idiopathic xanthomas.

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ULTRA-VIOLET ENERGY, ITS EFFECT AND INTENSITY AT VARIOUS LOCATIONS AND ALTITUDES *

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WITH direct proof that rickets occurs in the inverse proportion to the amount of ultra-violet energy reaching the child's body, together with the understanding of the fact that these short waves produce their effect by the activation of ergosterol, we may activate the ergosterol in our patient's body or we may activate the ergosterol itself and feed it to the patient. These established facts furnish a foundation for much valuable study.

The work of Hess, Brown, Howland, and Marriott and many others has put severe rickets, the rickets as described by the older authors, almost out of the picture, or at least in the class of preventable diseases. True there are many cases of mild rickets, but the deformity producing type need never be seen if we but use the agencies at our command.

I recall that when I first went to the southwest, almost 30 years ago, I noted the almost complete absence of rickets and discussed it with an elderly physician who had gone west ahead of the railroad, and he said, "Children who live in the open in our sunshine don't have rickets."

This study of the ultra-violet part of the spectrum, first begun with reference to rickets, has uncovered other possibilities of greater value and farther reaching effect.

With Viosterol (the commercial trade name given activated ergosterol, which is only bottled sunshine) we have a means of giving a measured dose. We know that these short waves stimulate calcium and phosphorus metabolism, and perhaps mineral metabolism in general. Competent observers have shown the beneficial effect of this product in parathyroid and in surgical tetany,^{1,2} in hastening the union of fractures,^{3,4} in benefiting acrodynia,⁵ psoriasis,⁶ urticaria,⁷ angioneurotic edema, eczema,⁸ asthma,⁹ and hay fever¹⁰; and in hastening the calcification of tuberculous lesions, thus checking their tendency to spread.^{11,12} Menschel¹³ reports reduction of fever, disappearance of night sweats, increase in weight, formation of scar tissue, lessened tendency to hemorrhage and general improvement in tuberculous patients. In pregnancy, relief of headaches, irritability, fatigue and stimulation of fetal development have been reported.^{14,15} Backaches, headaches, and nervousness accompanying menstruation are said to have been

* Read at the Montreal Meeting of the American College of Physicians, February 6, 1933.

† Dr. Rockwood, who worked out this method, devised this apparatus, and made these observations, died Nov. 23, 1932 before he had completed this study.

materially benefited^{1, 16}; and shortening of both bleeding and coagulation time has been observed.^{17, 18} Space will not permit the enumeration of all the benefits that have been reported.

We will soon begin to realize that the ultra-violet portion of ordinary sunshine which we use so little in modern life, shutting it out as we do from our homes, our offices and even our automobiles, has claims to be hailed as humanity's greatest boon.

In the study of the short wave part of the spectrum, much work has been done. Several different methods are used in making calculations and there is no way of evaluating the results of one method in terms of another.

Hill in England has made an extensive study using the acetone methylene blue method. He found that most of the short waves were lost in London, while in country places they were not. He found a reading of 41 in the Alps and the highest reading he obtained at Peppard Oxon was 23.

Frawley²⁰ made observations on the top of the Sierra Nevada's, at Fresno and at Santa Barbara using the acetone methylene blue method. Between the hours of 10 a.m. and 2 p.m. he found a fading of 11 units in the Sierra's, 9 units at Santa Barbara and 9 at Fresno. This method takes into account only the total amount of fading over a given period, but does not permit the estimation of the rate at any particular time.

Larsen and Godfrey²¹ made a very extensive series of observations near the Pacific coast using the oxalic acid method. They made observations at Riverside, San Francisco, Yakima, Seattle, Hong Kong and Honolulu, all these sites being near the sea and in low altitudes. Their observations ran over a period of several months and they found wide variations on days that were seemingly clear, so much alike that readings might have been expected to be about the same. These variations were probably due to differences in the amount of moisture in the upper atmosphere, which near the sea varies widely. Such stratification of the atmosphere does not perceptibly affect the clearness of the day. Their conclusions were that the short wave energy reaching the earth's surface in these locations varied so widely that in order to estimate intelligently the proper dosage of heliotherapy, observations should be made daily.

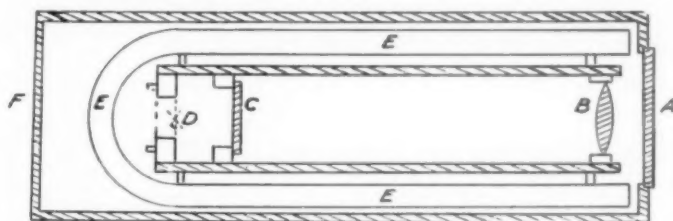
In its passage through the earth's atmosphere the solar radiation reaching the earth's surface is depleted by two causes: absorption and scattering. The absorption is due to gases which compose the atmosphere, and occurs in portions of the spectrum which are characteristic for each gas. Water vapor and carbon dioxide produce absorption chiefly in the infra-red; oxygen and ozone chiefly in the ultra-violet. In the antirachitic part of the ultra-violet there is a slight absorption by ozone which is nearly constant for all parts of the earth's surface, since the ozone is held in the layer of the atmosphere 30 to 40 miles above the surface of the earth.

The scattering of solar radiation can be divided into two parts: that due to dust particles, which is practically constant for all parts of the spectrum; and that due to atoms, molecules and ions of the gases, which is of

much greater importance in the ultra-violet than in the longer wave length regions, since the scattering varies as the inverse fourth power of the wave length.

The work we are reporting was done at the University of New Mexico in collaboration with the University of Michigan. In this work a study of the depletion of the solar radiation of a wave length of 3240 angstrom units was made. The selection of this wave length, 3240, was accomplished by means of a system of filters consisting of a Corex A glass filter and two silver films. The Corex A filter has a transmission band which extends from 2500 to 3900 angstrom units, with a broad maximum at 3200, while the silver has a narrow transmission band with a sharp maximum at 3200. These transmissions taken in connection with solar energy give a maximum transmission of energy at 3240. This energy was focused by means of a quartz lens on a four junction bismuth antimony surface thermopile, and the electrical current produced was measured by means of a Leeds and Northrup high sensitivity galvanometer.

The construction of the receiver and a photograph of the equipment set on a heliostat mounting are shown in figures 1 and 2.



Courtesy Rev. Scient. Instruments

FIG. 1. Cross section of receiver: (A) silvered Corex filter; (B) quartz lens; (C) silvered quartz plate; (D) thermocouple; (E) Dewar flask; (F) hard rubber case.

In this computation the amount of ultra-violet energy of a wave length of 3240 angstrom units is expressed in percentage of the radiation of that length reaching the outer atmosphere; thus if we arrive at a figure of 40 per cent, we mean that 40 per cent of the radiation wave length 3240 is received at the earth's surface and that 60 per cent is lost by absorption and scattering.

The method of computation takes us into higher mathematics and advanced physics and would be too technical for a paper of this nature. With this equipment, observations were made on the campus of the University of New Mexico at an elevation of 5100 feet; on the mesa seven miles east at an elevation of 5800 feet; at Carlito Springs in the Sandia Mountains at an elevation of 6750 feet; and at the Kiwanis Cabin on the crest of the Sandia Mountains at an elevation of 10,300 feet.

At 12:00 noon on the following dates, at the University Station, the readings were as follows:



FIG. 2. Photograph of apparatus set on heliostat mounting.

Oct. 17, 1931	33%	Dec. 5, 1931	24%
Oct. 28, 1931	33%	Dec. 11, 1931	23%
Nov. 14, 1931	26%	Dec. 23, 1931	21%
Nov. 25, 1931	24%	Dec. 30, 1931	23%
		Jan. 18, 1932	25%

This shows the effect of the increasing and decreasing air paths during the winter months.

Hourly readings were made at the University, October 28, 1931 from 10:00 a.m. to 3:00 p.m.

10:00 a.m.	28%	1:00 p.m.	25%
11:00 a.m.	32%	2:00 p.m.	21%
12:00 noon	33%	3:00 p.m.	12%

This shows the effect of the increasing and diminishing air paths as the sun approaches and leaves the meridian.

At Sunset View Station, at the mouth of the canyon, elevation 5,810 feet, the readings were as follows:

January 8, 1932 from 1:30 p.m. to 3:30 p.m.:

1:30 p.m.	30.9%	2:30 p.m.	21.8%
2:00 p.m.	27.8%	3:00 p.m.	18.4%

January 18, 1932 from 11:30 a.m. to 3:00 p.m. at same station:

11:30 a.m.	29.8%	1:30 p.m.	28.6%
12:00 noon	31.0%	2:00 p.m.	25.5%
12:30 p.m.	31.7%	2:30 p.m.	21.3%
1:00 p.m.	30.3%	3:00 p.m.	17.4%

At Carlito Springs, elevation 6,850 feet, the following readings were obtained.

November 14, 1931 from 10:30 a.m. to 3:00 p.m.:

10:30 a.m.	33.9%	1:00 p.m.	36.3%
11:00 a.m.	36.3%	1:30 p.m.	31.4%
11:30 a.m.	39.2%	2:00 p.m.	30.5%
12:00 noon	38.8%	2:30 p.m.	28.0%
12:30 p.m.	37.7%	3:00 p.m.	20.7%

It is noteworthy that the highest reading on this day was at 11:30 a.m. whereas it is usually at 12:30 p.m.

On December 5, 1931 at Carlito Springs the readings were as follows:

11:00 a.m.	31.9%	1:00 p.m.	30.3%
11:30 a.m.	33.9%	1:30 p.m.	26.4%
12:00 noon	31.9%	2:00 p.m.	26.8%
12:30 p.m.	30.7%	2:30 p.m.	21.1%
		3:00 p.m.	15.0%

Here again the highest reading was obtained at 11:30 a.m. and the 2:00 p.m. reading was higher than the 1:30 p.m. reading.

The following readings were taken at the Kiwanis Cabin on the crest of the Sandia Mountains at 10,300 feet elevation on October 30, 1931 from 10:30 a.m. to 3:30 p.m.

10:30 a.m.	39%	1:00 p.m.	43%
11:00 a.m.	40%	1:30 p.m.	40%
11:30 a.m.	43%	2:00 p.m.	35%
12:00 noon	46%	2:30 p.m.	31%
12:30 p.m.	47%	3:00 p.m.	25%
		3:30 p.m.	16%

and on October 30, 1932 at the same station:

10:30 a.m.	33%	1:00 p.m.	36.2%
11:00 a.m.	34%	1:30 p.m.	34.0%
11:30 a.m.	36.2%	2:00 p.m.	29.8%
12:00 noon	39.2%	2:30 p.m.	26.6%
12:30 p.m.	40.1%	3:00 p.m.	21.1%
		3:30 p.m.	13.8%

The larger percentages at the increased elevation are due to the fact that the light passes through a smaller amount of air, and that there is very little water vapor at these high altitudes, and a negligible amount of dust. The lower readings at the campus show the effect of dust, smoke and water vapor.

On November 5, 1932 the following study was made. An airplane was sent up to an altitude of 12,000 feet, flying over the vicinity in which observations were being made on the ground. Beginning at 11:45 an estimate of the amount of moisture in the air was made at each 1,000 foot level as the airplane descended, using the dry and wet bulb thermometers. This took only three minutes at each level so that very little time was lost between readings. A reading was also taken on the ground. From this data we calculated (using Rockwood's ²² formulae), the per cent of transmission one might expect at different altitudes. The calculations gave results as follows:

5,000 feet	27.3%	9,000 feet	37.6%
6,000 feet	30.6%	10,000 feet	39.3%
7,000 feet	32.7%	11,000 feet	41.5%
8,000 feet	35.5%	12,000 feet	42.8%

A direct determination from the ground, altitude 5,050 feet, gave a reading of 29.0 per cent. Only one direct reading was taken because the observer was especially interested in the infra-red determinations during the flight.

We also calculated the per cent of transmission one might expect at the different altitudes if the air were dry, with the following results:

5,000 feet	35.3%	9,000 feet	40.7%
6,000 feet	36.7%	10,000 feet	42.1%
7,000 feet	38.1%	11,000 feet	43.4%
8,000 feet	39.4%	12,000 feet	44.7%

By comparing these results we find at 5,000 feet a difference of 12 per cent between dry and moist air, and at 12,000 feet the difference is only 1.9 per cent and the curves are rapidly approaching each other (see figure 3).

The following readings were taken on an automobile trip from Ann Arbor, Michigan up to Quebec, and back down through Vermont, New York, Pennsylvania, West Virginia, Tennessee, Oklahoma, and Texas. Readings were taken only on fairly cloudless days when it would be possible to get a fair estimate. A wait of three days was made in Oklahoma but it was too cloudy to get a fair reading, and as time was limited the journey had to be resumed without obtaining a reading.

A reading was taken in the Plains of Abraham, August 22, 1932:

9:00 a.m.	24.5%	10:20 a.m.	27.3%
9:30 a.m.	25.4%	10:40 a.m.	30.4%

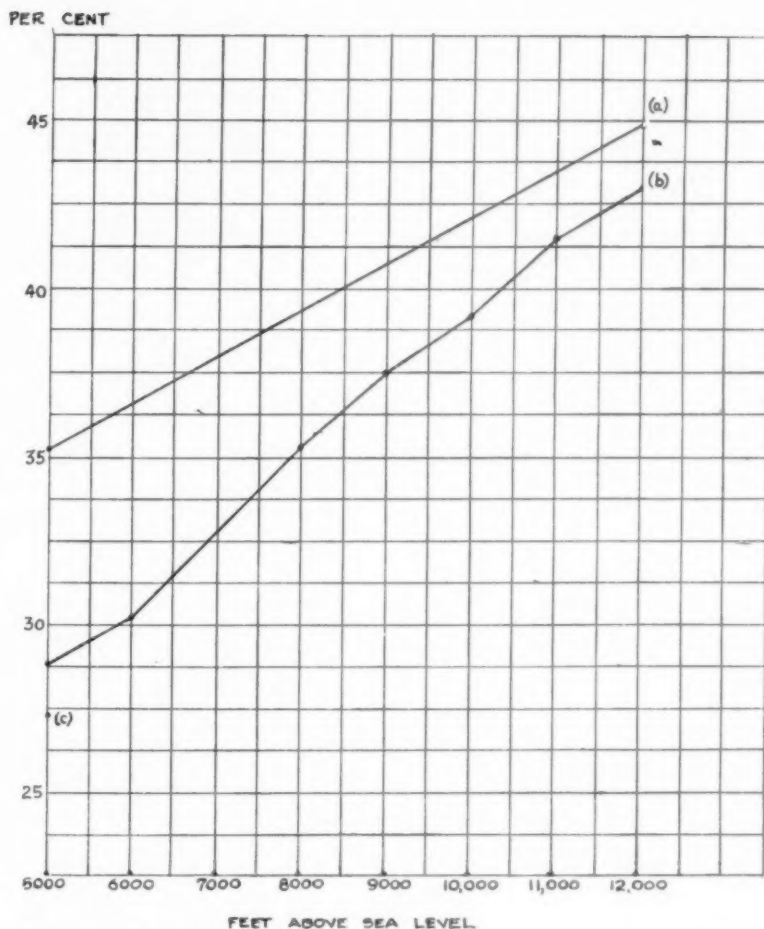


FIG. 3. (a) Dry air (calculated) Rockwood's formulae; (b) moist air (calculated from vapor pressure at different altitudes); (c) direct determination.

The results were 11 per cent lower than a reading at the Kiwanis Cabin on November 6.

At Norton Mills on the Vermont-Quebec line:

9:00 a.m.	23.6%	10:30 a.m.	33.0%
9:45 a.m.	27.5%	11:05 a.m.	36.3%
		12:00 noon	37.8%

The next clear weather was encountered at Romney, West Virginia, August 26, 1932. This reading shows the small percentages in the early morning:

7:00 a.m.	0.9%	9:55 a.m.	21.9%
8:00 a.m.	7.7%	10:40 a.m.	25.4%
8:35 a.m.	13.2%	11:15 a.m.	26.7%
9:15 a.m.	17.4%	11:55 a.m.	27.0%

The next reading was taken on Vanderbilt Campus, Nashville, Tennessee August 29, 1932.

7:45 a.m.	13.6%	10:20 a.m.	33.3%
8:35 a.m.	21.3%	12:15 p.m.	31.0%
9:15 a.m.	27.0%		

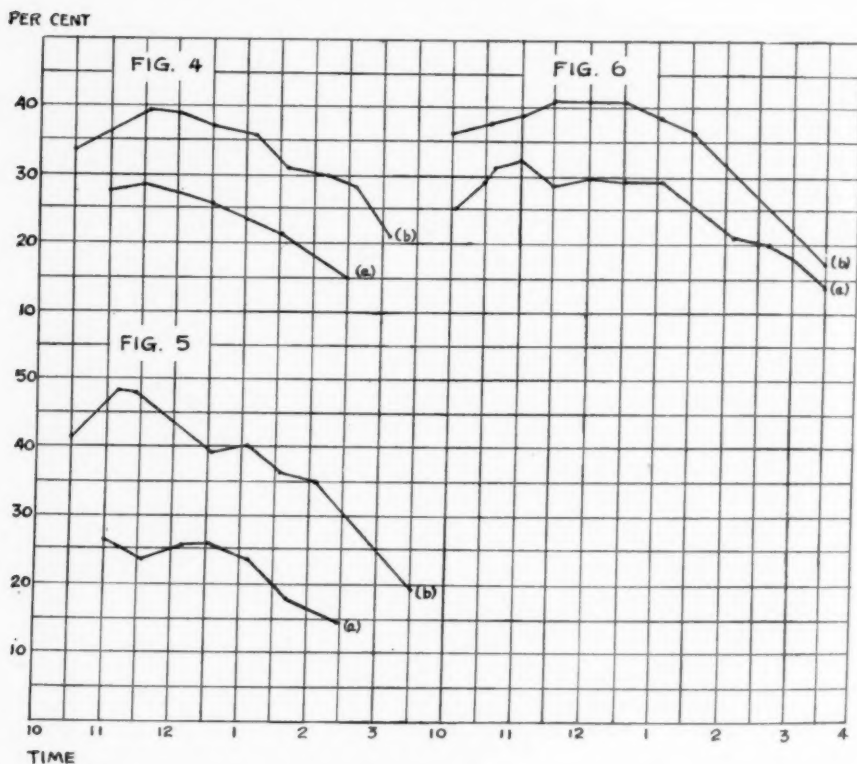


FIG. 4. Observations Nov. 14, 1931. (a) University Station, elevation 5,100 ft.; (b) Carlito Springs, elevation 6,750 ft.

FIG. 5. Observations Nov. 6, 1931. (a) University Station, elevation 5,100 ft.; (b) Kiwanis Cabin, elevation 10,300 ft.

FIG. 6. Observations; average of several days. (a) University Station; (b) Kiwanis Cabin.

At Amarillo, Texas, September 3, 1932 the readings were:

2:00 p.m.	44.0%	4:00 p.m.	12.3%
2:45 p.m.	32.2%	4:25 p.m.	7.4%
3:30 p.m.	21.3%		

Thus we see that as we get up onto the western plateau the readings are higher.

Readings at Colorado Springs yielded about the same results as those at the University of New Mexico Station, and Pettit's readings at Mount

Wilson Observatory run about the same as our readings at the crest of the Sandia Mountains. This is perhaps more clearly shown by the charts. (See figures 4, 5, and 6.) We see that at Sunset View the readings are uniformly a little higher than those at the University; at Carlito Springs they go still higher; and at the crest the readings are consistently higher.

These findings harmonize with the findings of Hill, Frawley and Pettit, and while the study does not embrace enough locations over a sufficiently long period of time, the results point definitely to the conclusion that in high altitudes in arid and semi-arid regions, the percentage of short waves reaching the earth's surface is much higher than in low altitudes where the humidity is greater, and that density of population with its attendant increase of smoke and dust, also reduces the amount of health-giving rays received from the sun. The old idea that rickets was a condition which increased in proportion to the density of the population was in part true.

For ages it has been the practice of people in search of health, rest, relaxation and recuperation to seek the high, dry, arid and semi-arid regions, not knowing why they did so except that it was customary and that they felt a deep-rooted conviction that they were benefited by so doing.

We now find the scientific justification of this ancient practice. As in the case of many established practices that have been followed empirically for many generations, when we are able to get down to the facts we find ample scientific reason and explanation.

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THE INCIDENCE OF HYPERTENSION AMONG URBAN JAPANESE *

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CADBURY,¹ Cruickshank,³ Kilborn,¹² and others have called attention to the fact that the average blood pressure of the Chinese is lower than the average of Occidentals, the difference being about 10 mm. of mercury. Foster⁶ found, in his experience, that hypertension is rare in the Chinese. He found about 20 patients whose systolic blood pressures were more than 160 mm., among about 4000 patients examined on the medical service of the Hunan-Yale Hospital. Harris⁹ was of a similar opinion concerning the incidence of hypertension in Chinese. Foster⁶ and Tung¹⁸ reported that the blood pressures of Occidentals, mostly Americans, living in China, were about the same as those of the local Chinese, and that the blood pressure of the majority of these persons was lower in China than it was in America. Harris, however, did not find that the blood pressures of Europeans and Americans living in China, were lower than they would have been expected to be if the subjects had continued to live in Europe or America.

Musgrave and Sison¹³ found the blood pressures of Filipinos to be lower than the average given for Americans and Europeans living in their own countries, and also they found that the blood pressures of Americans apparently were lowered following long-continued residence in the Philippines. On the contrary, Chamberlain² reported that the blood pressures of Americans residing in the Philippines differed but little, if any, from the average in the United States, and that the average pressure of Filipinos was practically identical to that of Americans.

Although the reports from the Philippines concerning the blood pressures of Filipinos, and of Americans residing there, are conflicting, most of the investigators in China agree that the average blood pressure of the Chinese is lower than the average of Occidentals living in their own countries, and that hypertension is rare among the Chinese. The causative factors of such relatively low blood pressures among the Chinese, however, remain open to discussion. Various causes have been suggested: racial predisposition, a climate which lowers vasomotor tone, simplicity of life in China, absence of nervous strain, and so forth. If the blood pressures of Occidentals become lower following prolonged sojourn in China, as has been reported by Foster and Tung, the climate of China, or the simplicity of life there, may be responsible. If such a change in blood pressure does not occur during the sojourn of Occidentals in China, and if hypertension

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From the St. Luke's International Hospital, Tokyo, Japan.

among them is as common when they live in China as when they live in Western countries, as has been found by Harris, the hypotension of the Chinese may be regarded as due to such factors as constitution of the Chinese, their mode of life, or their diet.

For those who have an interest in racial blood pressure and in the etiology of hypertension in general, it might be desirable to present data on the average blood pressure of the Japanese, and on the frequency of hypertension in Japan. Ishioka,¹⁰ chief medical director of the First Mutual Life Insurance Company, Tokyo, Japan, after a study of the records of accepted risks, has stated that the average systolic blood pressure of healthy Japanese adults is slightly lower, and the average diastolic pressure decidedly lower, than that of Americans of corresponding age. Table 1 shows the

TABLE I

Average Blood Pressures in mm. of Mercury of Healthy Japanese Men, Resident in Japan and of Healthy American Men, Resident in the United States of America

Age, years	Japanese (Ishioka ¹⁰)		Americans (Symonds ¹⁷)	
	Systolic	Diastolic	Systolic	Diastolic
15 to 19	112.7	67.9	123.5	79.5
20 to 24	121.0	72.3	124.2	80.5
25 to 29	120.7	73.5	124.5	81.5
30 to 34	122.4	74.5	125.1	82.3
35 to 39	123.5	76.0	125.3	83.3
40 to 44	126.1	76.5	126.4	84.0
45 to 49	127.3	77.1	128.2	84.7
50 to 54	133.9	80.9	130.2	85.9
55 to 59			133.5	86.8

(The diastolic pressure was taken at the end of the fourth phase by Ishioka¹⁰ as well as by Symonds.¹⁷)

average blood pressures of healthy Japanese males of various ages resident in Japan, as reported by Ishioka, compared with the average blood pressures of healthy American males (of all builds), resident in the United States of America, as published by Symonds.¹⁷ As regards the incidence of hypertension among the Japanese, Norris¹⁴ stated, according to Volhard: "The Japanese are rarely the subjects of arterial hypertension, a fact which suggests that diet and mode of life may account for this relative immunity." It has been common experience among physicians in Japan, however, to find hypertension fairly frequently among the Japanese, ever since portable sphygmomanometers have been extensively used. Such information as that of Volhard, and of others, might have been derived from clinical experiences at a time when handy instruments for estimating blood pressure were not so extensively used as at the present, or from unsatisfactory statistical data. Little information on this point has been found in the medical literature of Japan.

We have derived the data about to be presented here from the records of the out-patient department of St. Luke's International Hospital, Tokyo,

Japan. From 1926 to 1932, we determined the blood pressures of 16,393 Japanese. In the first two years, 1926 and 1927, we determined the blood pressures of all new patients examined in the medical social service section of the out-patient department. In the last five years, 1928 to 1932, all new patients, including all pay patients, were examined. Out-patients in the social service section were all poor; the majority of them were poorly paid wage-earners, and their standard of living was decidedly lower than that of patients who could pay ordinary rates for medical examination and treatment. The average income of the out-patients in the medical social service section was as low as 684 yen a year for a family of five, whereas 977 yen a year is the minimal amount needed for support of a family of this size in the part of the city from which our poor patients come. This has been shown in the estimates made by one of the social workers in our hospital.

The blood pressures of all patients were taken after they had rested supine for about 10 minutes. The sphygmomanometers used were Baumanometers (mercury) or Tycos instruments (aneroid); the latter were tested frequently against a standard mercury manometer to assure that they were accurate. The auscultatory method was adopted, while the tactile method was used to verify the systolic pressure. The diastolic pressure was taken at the beginning of the fourth phase, when the clear sound became muffled.

The diagnosis of hypertension was made if a patient persistently had a systolic pressure of more than 160 mm. of mercury, or if a patient had a diastolic pressure of more than 100 mm. even though the systolic pressure was only moderately elevated. There were 1,306 cases of hypertension among 16,393 out-patients thus examined, or 8.0 per cent. Stated otherwise, 491 of 6,066 men (8.1 per cent) and 815 of 10,327 women (7.9 per cent) had hypertension.

Of 10,058 poor patients, 943 (9.4 per cent) had hypertension: 325 of 3,530 men (9.2 per cent), and 618 of 6,528 women (9.5 per cent). There were 363 cases of hypertension among 6,335 pay patients (5.7 per cent): 166 of 2,536 men (6.5 per cent), and 197 of 3,799 women (5.2 per cent). The incidence of hypertension among poor patients was considerably higher than among pay patients.

Tables 2 and 3 show the incidence of hypertension by half decades of life among, respectively, poor patients and pay patients. Among poor patients, hypertension occurred in a frequency of more than 10 per cent, at as early an age period as 36 to 40 years, whereas among pay patients a percentage of more than 10 per cent was found only after the age of 45 years. At later age periods than those just mentioned, the incidence of hypertension for men and for women of both groups gradually and progressively rose. To summarize, the incidence of hypertension was relatively low in early adult life, and higher in late adult life, and it was higher among poor patients than among pay patients. The incidence among poor patients began to rise at an earlier age than it did among pay patients.

TABLE II

Incidence of Hypertension Among Poor Out-Patients, St. Luke's International Hospital, Tokyo, Japan (1926-1932)

Age, years	Patients examined				Hypertension Per cent	
	Patients with hypertension		All out- patients			
	Men	Women	Men	Women	Men	Women
13 to 15	1	1	215	235	0.5	0.4
16 to 20	13	10	606	713	2.1	1.4
21 to 25	18	61	637	1642	2.8	3.7
26 to 30	18	82	505	1350	3.6	6.1
31 to 35	10	75	355	847	2.8	8.9
36 to 40	34	64	290	532	11.7	12.3
41 to 45	32	54	229	338	14.0	16.0
46 to 50	40	49	212	294	18.9	16.7
51 to 55	48	67	180	229	26.6	29.2
56 to 60	37	47	113	136	32.7	34.6
61 to 65	39	49	102	107	38.2	45.8
66 to 70	21	26	55	59	38.2	44.1
71 to 80	14	33	31	46	45.2	71.8
13 to 80	325	618	3530	6528	9.2	9.5

TABLE III

Incidence of Hypertension Among Pay Out-Patients, St. Luke's International Hospital, Tokyo Japan (1928-1932)

Age, years	Patients examined				Hypertension Per cent	
	Patients with hypertension		All out- patients			
	Men	Women	Men	Women	Men	Women
13 to 15	0	0	46	63	0	0.0
16 to 20	4	0	396	416	1.0	0.0
21 to 25	8	13	432	903	1.9	1.4
26 to 30	9	11	390	712	2.3	1.5
31 to 35	11	20	336	619	3.3	3.2
36 to 40	6	26	214	368	2.8	7.1
41 to 45	10	21	189	245	5.3	8.6
46 to 50	21	32	170	192	12.4	16.7
51 to 55	39	24	154	123	25.3	19.5
56 to 60	13	17	76	70	17.1	24.3
61 to 65	26	18	69	51	37.7	35.3
66 to 70	11	7	36	21	30.6	33.3
71 to 80	8	8	28	16	28.6	50.0
13 to 80	166	197	2536	3799	6.5	5.2

In the examination of the patients with hypertension, the attempt was made to obtain some information on matters which have been supposed to concern the etiology of hypertension. The family histories of patients with hypertension have been studied to determine whether there was any hereditary predisposition to hypertensive cardiovascular diseases. So far as the patients have informed us, cerebral apoplexy occurred in 21 per cent of the families, hemiplegia in 2.5 per cent, and sudden cardiac death in 4.8 per cent.

The diet of the Japanese consists mainly of rice, vegetables, and fish. The Government Food Committee reported that the average daily food of the Japanese consists of 85 per cent carbohydrate, 3 per cent fat, and 12 per cent proteins. Animal proteins, mainly those from fish, comprise not more than 15 per cent of the total amount of proteins. It was very difficult to learn what actually had been eaten by the patients, but there is little doubt that at least the poor patients, among whom the incidence of hypertension was comparatively high, ate very little meat for meat is fairly expensive. Only about 0.4 per cent claimed a preference for meat. About 32 per cent of patients with hypertension used alcoholic beverages, but only about 7.5 per cent drank to excess. About 45 per cent of the patients used tobacco, but only 1.5 per cent used it in excessive amounts.

The body weight of about 65 per cent of the patients with hypertension was within the normal range. Twenty-four per cent of the total number were rather thin, whereas only 10 per cent were obese.

It was not rare to find evidence of syphilis among patients with hypertension. Wassermann tests were made of the blood of 614 patients with hypertension, and 148 of them, or 24.2 per cent, were positive. However, of 3,263 Wassermann tests of patients without hypertension, who were in the hospital, 821 (25.1 per cent) were positive, which compares fairly closely with the incidence among patients with hypertension. Of 1,635 women admitted to the maternity ward of the hospital, 172 (10.5 per cent) gave serologic evidence of syphilis. The majority of these women were from the same class of people as those who live in the district of the city from which the poor patients with hypertension came. This 10.5 per cent may indicate the incidence of syphilis among healthy women of this class, but may not be adopted as a control in our study of patients with hypertension, because a higher incidence of syphilis is usually found among patients than among apparently healthy people.

Urinalysis made in 746 cases of hypertension, in recent years, revealed nephritis in 163 (21.9 per cent). Albumin, erythrocytes and casts, were found in the examination of the urine of 19.7 per cent of poor male patients and of 25 per cent of poor female patients; and also, in the examination of the urine of 23.2 per cent of male pay patients and 14.6 per cent of female pay patients. About 78 per cent of our patients with hypertension were free from any clinical evidence of inflammatory disease of the kidneys. Of our patients with hypertension, 22.3 per cent had nocturia. Blood chemical studies of the majority of the patients with hypertension gave negative results. The non-protein-nitrogen of the blood of some of the patients examined was increased at the terminal stage of the disease.

The fate of the patients with hypertension was studied by repeated observation in the out-patient department or by continued observation in the ward. When they failed to return to the clinic, visiting nurses were sent to follow them up. In 1926 and 1927 repeated determinations were made of the blood pressures of 70 men and 119 women with hypertension. In

the course of medical treatment, mainly simple administration of bromides, there was slight, gradual subsidence, to a little less than 160 mm. in the blood pressure of a number of these patients. Of the 70 men, 22.7 per cent, and of the 119 women, 11 per cent, died in the course of the period of observation. The male patients were observed for an average of 268 days, and the female patients for an average of 331 days. The highest mortality rate was in the age period 50 to 60 years. The mortality rate was 8.1 per cent among patients whose systolic blood pressure ranged from 160 mm. to 180 mm.; 14.8 per cent among those whose systolic blood pressure ranged from 180 mm. to 200 mm., and as high as 26.2 per cent among those whose systolic blood pressure was continuously higher than 200 mm. The immediate cause of death was considered to be cerebral hemorrhage in 25.8 per cent of the cases from which the foregoing figures were derived; cardiac failure in 29 per cent, and uremia in 22.6 per cent. Other intercurrent diseases were the causes of death in 9.7 per cent. In the remaining cases no information was secured on this point. In 1928 and 1929, repeated determinations of blood pressure could be made of only 18 males and 51 females. The hypertension of 16.7 per cent of the men and of 27.5 per cent of the women gradually subsided. Of 393 patients who were diagnosed as hypertension during these two years, 132 were followed for a considerable time; the average was 347 days for male patients and 413 days for female patients. The visiting nurses reported that 11 of 45 men and four of 87 women died.

COMMENT

It is very difficult to compare the incidence of hypertension in one country with that in any other country, because few data are available that show directly the incidence of hypertension in the population at large. The reports of life insurance companies concerning the results of medical examinations of applicants may show the incidence of hypertension among people who are presumably in good health, unconscious of physical impairment, for most of those with known cardiovascular or renal diseases do not apply for life insurance. Some people of the latter group will present themselves to hospitals or to medical practitioners if they become ill. But it must be remembered that many persons are not interested in life insurance, and many others who are actually ill are not conscious of physical impairment; among the latter are patients with hypertension of insidious onset. If data from the above-mentioned two sources are combined, however, some impression may be gained of the incidence of hypertension in the community.

Ishioka,¹⁰ of the First Mutual Life Insurance Company, Tokyo, reported that 60 cases of hypertension were discovered in the medical examination of 4,537 Japanese applicants for life insurance, an incidence of 1.32 per cent. He considered that hypertension existed, if the systolic blood pressure was consistently more than 15 mm. above the average for persons of given age and sex. Among the persons with hypertension identi-

fied on this basis, average blood pressures within the various age groups varied from 153 to 189 mm., mostly more than 160 mm. As to the distribution by age of all applicants examined, 83.6 per cent were less than 40 years of age, and 16.4 per cent more than 40 years of age. The figures of Ishioka, just given, may be comparable with those of Frost⁷ in America. Frost studied the records of the medical department of the New England Mutual Life Insurance Company, and reported that among 146,992 Americans examined over a period of six years, 1919 to 1924, there were 2,568 cases of hypertension, an incidence of 1.74 per cent. Any person whose systolic pressure persistently was more than 15 mm. above the appropriate average pressure, and whose diastolic pressure was more than 10 mm. above the appropriate average pressure, was considered by him to have hypertension. Of all applicants examined, 76 per cent were aged less than 40 years and 24 per cent more than 40 years. The incidence of 1.32 per cent among Japanese is a little lower than that of 1.74 among Americans. From this comparison only, however, it can hardly be concluded that the incidence of hypertension among Japanese is lower than that among Americans, if it is taken into consideration that the comparison is between the results of two investigations carried out on materials of different age distribution.

Concerning the incidence of hypertension among patients in hospital, there has been little information in the medical literature of Japan. K. Yasui and S. Mori,¹⁹ having determined the blood pressures of all patients admitted to the Kyoundo Hospital, Tokyo, during four years, 1925 to 1928, found that of 7,365 patients, the systolic blood pressures of 2,689 (36.5 per cent) were more than 140 mm. and of 1,218 of these more than 180 mm. Of all patients with hypertension, 43 per cent had nephritis. These data may be compared with those which have been reported by Gelman,⁸ and by Saller¹⁶ from Europe. Gelman, who had examined 3,761 patients in the Obuch Institute for Occupational Diseases at Moscow, reported that there were 344 whose systolic blood pressures were more than 140 mm., an incidence of 9.1 per cent. Saller found systolic blood pressures of more than 143 mm. in 685 of 4,128 cases (16.6 per cent) at the Universitäts-Klinik of Kiel. The incidence of hypertension in the patients of one of the hospitals in Tokyo, differs markedly from that in the European hospitals named. Even when cases of nephritis with hypertension have been excluded, the number of cases of hypertension in the Japanese hospital would amount to 19.3 per cent. Such a high incidence may partly be attributed to the fact that the cardiovascular clinic of this hospital is well known among people of the city, and attracts more patients with hypertension than other hospitals attract.

Janeway,¹¹ in his study of hypertensive cardiovascular disease in Americans, found that 870 of 7,872 adult patients more than 20 years of age (11.1 per cent), at some time had systolic blood pressures of 165 mm. or more. Of all patients examined by us, until the end of 1931, in the outpatient department of our hospital in Tokyo, 11,258 were aged more than

20 years. Of 7,303 adults of poor families, 801 (11 per cent) had systolic pressures of more than 165 mm., and diastolic pressures of more than 100 mm. Similar pressures were displayed by 241 of 3,955 pay patients (6.1 per cent).

Foster⁶ in his study of the incidence of hypertension in the Chinese, referred to the report of the Peter Bent Brigham Hospital, Boston, which showed that there were 236 cases of essential hypertension and 146 cases of chronic nephritis with hypertension among 4,940 patients on the medical service of the hospital in the two years, 1918 and 1919. The systolic blood pressures in these cases were more than 160 mm. The incidence of hypertension among the patients included in the report quoted by Foster, then, was 7.7 per cent. Among 16,393 Japanese examined in our hospital in Tokyo, 1,306 had hypertension, diagnosed by a standard similar to that used at Peter Bent Brigham Hospital; this gives an incidence of 8 per cent, which is fairly close to the rate of 7.7 per cent found in Boston.

Riseman and Weiss¹⁵ stated that 2.9 per cent of male patients and 6.6 per cent of female patients admitted to the medical out-patient department of the Boston City Hospital in the 45 months from April 1925 to December 1928, had arterial hypertension. The diagnosis of hypertension was made by them on 1,620 of 28,906 new patients examined. Of the patients with hypertension, the systolic pressure was more than 160 mm. in 91.6 per cent, and less than 150 mm. in 3.1 per cent. The diastolic pressures were more than 100 mm. in 66.1 per cent. Of 1,620 patients with hypertension, 281 exhibited evidence of impaired renal and cardiac function, or of cerebral hemorrhage. The incidence of hypertension of 2.9 per cent, for male patients in the Boston City Hospital, is considerably lower than our rate for male poor patients, 9.2 per cent, or our rate of 6.5 per cent for male pay patients, whereas the rate of 6.6 per cent for female patients in Boston falls between our two rates for hypertension among female Japanese in our hospital in Tokyo: namely, lower than 9.5 per cent for poor women patients and higher than 5.2 per cent for pay women patients. It is evident that hypertension is predominant in the later years of life. Therefore, if a comparatively large number of elderly patients would happen to present themselves for examination in a certain hospital, there might be encountered a larger number of cases of hypertension than in other hospitals. In the out-patient department of the Boston City Hospital, 54.3 per cent of the male patients, and 66.9 per cent of the female patients were aged less than 45 years. In our hospital 79.7 per cent of all male patients and 86.9 per cent of all female patients examined in the out-patient department were less than 45 years of age.

Although a diet high in protein used to be mentioned as one of the factors responsible for inducing the hypertensive cardiovascular disturbances, it is of interest to note that hypertension was not rare among our charity patients whose diet is low in protein.

As one of the factors that influence the incidence of hypertension, racial

difference has been pointed out by some authors. However, of the mixture of Oriental races of which the Japanese people are composed, no race which is anthropologically different from the Chinese is predominant; yet hypertension is more frequently found among the Japanese than among the Chinese. Foster's finding at the Hunan-Yale Hospital has been mentioned earlier in this paper. As to climate, that of Tokyo differs not much from that of many cities in China. The diet of the Japanese, especially that of poor people, is rather lower in protein than that of the Chinese.

Fishberg⁵ noted that hypertension is not rare among negroes in New York City, while Donnison⁴ pointed out the fact that hypertension scarcely occurs among negroes living in a primitive state in Africa. Among the patients examined by us, hypertension was found to occur more frequently and at earlier periods of life among poor people than among those able to pay for medical attention. The majority of the charity patients are poorly paid wage-earners who are struggling for existence; their daily work involves much nervous and physical strain. Living in a thickly populated, factory district of the city, they are not at all protected against the various infections that may affect the kidneys or the cardiovascular system. If the incidence of hypertension among urban Japanese really differs from that among the Chinese, the difference should not be attributed to racial peculiarities but rather might be explained as being due to the different industrial environment and the different attitude of the people to it.

SUMMARY

Comparative studies of the incidence of hypertension among Japanese and among Americans or Europeans, based on statistical data derived from the reports of life insurance companies and from hospitals in Japan and in America or Europe, indicate that hypertension is by no means rare among urban Japanese, since it is found nearly as frequently as among Americans or Europeans. If the incidence of hypertension among urban Japanese is higher than among Chinese, the difference should not be explained as being due to racial peculiarities, but rather it might be attributed to the more intricately organized industrial life of Japan, and the reaction of the Japanese to the conditions such a life entails.

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GASTROINTESTINAL ALLERGY IN CHILDREN *

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THE PURPOSE of this discussion is to consider some of the gastrointestinal allergic manifestations in children and to suggest their relationship and similarity to certain symptoms which occur in adults and which are not generally considered as having an allergic basis. In this brief discussion no attempt will be made to consider extra-gastrointestinal allergic signs and symptoms, such as angioneurotic edema, urticaria, eczema, migraine, allergic rhinitis, asthma, and so forth, any one of which may result from the ingestion of food to which the individual is over sensitive; but, only evidences of local allergic irritation to the gastrointestinal tract will be taken up.

GASTRIC MANIFESTATIONS

Not infrequently one sees infants who begin to vomit as soon as they take food (breast milk). Others may take breast milk well and begin to vomit when cow's milk is begun. Still others do well on milk and begin to vomit only when other articles of food are added to their diet, such as eggs, orange juice, chocolate, nuts, and so forth. In other words, one may encounter allergic vomiting at any stage of childhood, depending upon when the exciting substance which is responsible for the symptom of vomiting becomes a part of the diet. I do not mean to give the impression that vomiting is a very common symptom of allergy, or that allergy figures very prominently as a cause when we consider all the vomiting that occurs in children. Just as allergy produces many symptoms other than vomiting, so vomiting has many causes other than allergy. The point is that when allergy is the cause of vomiting, the vomiting tends to be of a persistent nature and no relief is obtained unless the causative factor is recognized and removed completely or partially, or unless chance removes the cause for us, which not infrequently happens.

The earliest type of allergic vomiting which we see is that in small infants which begins when the infant first takes food, or soon after. In these infants hypertrophic stenosis of the pylorus is nearly always thought to be the cause of the vomiting. And of course, probably in the majority of instances of persistent vomiting at this period, it is the cause. However, I have seen a number of infants with early persistent vomiting whose condition had been diagnosed hypertrophic stenosis of the pylorus but whose symptoms were relieved only when it was found that they were sensitive to milk and when the cause of trouble was removed. I also know of five infants who were operated on in various hospitals for hypertrophic stenosis

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of the pylorus, but were found to have no hypertrophy. Later their symptoms were relieved when the allergic nature of the condition was discovered and the causative factor was removed.

A few months further up the scale of infancy we not infrequently encounter vomiting when new articles of food are added to the diet. This of course does not necessarily mean that the child is over sensitive to the new food unless the vomiting occurs each time the food is given, and even then, one looks for additional evidence to prove allergy as the cause. A family history of allergy in the mother, in the father, or in both is usually present when the infant presents this particular symptom of allergy. A positive skin test to an extract of the food is usually present. This, however, is not always so, just as in adults. Other allergic manifestations in the patient such as urticaria or eczema should be sought for, but such skin manifestations do not usually occur coincidentally with the gastrointestinal manifestations of allergy. In older children one may get a history of previous skin manifestations. Finally, strong supporting evidence of the true nature of the condition is obtained if there is a cessation of symptoms upon eliminating the suspected food from the diet, and if there is a recurrence of symptoms when the food is again added to the diet. Unfortunately the situation not infrequently is complicated by the fact that there is in the diet more than one food to which the child is sensitive.

It is usually later on in childhood that we meet the familiar condition called cyclic or recurrent vomiting. Attacks of cyclic or recurrent vomiting may not always be due to allergy but I have had occasion in the case of several children to prove their allergic basis. For example, one 10 year old girl had had a number of attacks of cyclic vomiting. She was found to be skin sensitive to milk. As long as milk and milk products were left out of the diet there was no trouble. Another child had attacks once a year when he went to the circus. The attacks were attributed to excitement and exhaustion, but on further questioning it was found that he ate peanuts only during his visit to the circus, and when tested to peanuts he was found to be sensitive. The parents doubted the validity of our suggestion that peanuts were probably responsible for his trouble and somewhat later gave him peanuts. A severe attack followed. By accident the experiment was repeated several times with the same results. There is further evidence and support of the allergic nature of cyclic vomiting in that a number of the adults who suffer with migraine give a history of cyclic vomiting during childhood. This of course presumes that migraine is an allergic manifestation.

INTESTINAL MANIFESTATIONS

Again, early in infancy, one sees children who do not vomit but who have severe intestinal symptoms, such as colic, frequent bowel movements containing mucus, and the passage of a great deal of gas by bowel. The frequent movements are not watery as in diarrhea, but are soft, are apt to be

small, and nearly always contain mucus. The colic mentioned here is genuine colic and not mere hunger pains which so frequently are called colic. This type of manifestation is similar to much of the mucous colitis of adults. In children, however, one seldom sees the spastic type of colitis. These children gain weight well and develop well if given an adequate amount of food but almost run the family crazy until relief from their pain is obtained by finding the cause of their trouble and removing it. As opposed to other children who may temporarily have similar symptoms due to other causes, these small infants are not ill but are merely very uncomfortable. The allergic nature of this condition is readily suspected if one has had previous experience with such infants, but proof of the diagnosis is to be obtained only by more or less the same methods as those indicated above in connection with vomiting. Symptoms like these may occur during any stage of childhood and even in adults. For example, a small child who had suffered for two months with the above mentioned symptoms was found to be sensitive to milk and was completely relieved when he was placed on a dried milk preparation which of course had been heated. Various fresh milk preparations had been tried with no benefit. The probable explanation of the relief which these children often get when placed on a milk preparation which has been subjected to prolonged heating is that there are two factors in milk to which they may become sensitive and one is apparently heat labile. This is the explanation recently offered by Lewis and Hayden.¹ Another older child (12 years of age) passed a great deal of gas, had soft bowel movements containing much mucus, and had colicky pains in the abdomen. He was found to be sensitive to chocolate and on repeated occasions later his symptoms recurred following the ingestion of chocolate. Still another patient (an adult) who had complained of marked abdominal pain for three years, and for a year had had typical severe mucous colitis symptoms, was found to be sensitive to milk and on the removal of milk and all milk products from his diet all symptoms disappeared and his weight rapidly rose from 130 to 200 pounds. He was six feet two inches tall, very much under weight and had made milk and various milk drinks a constant part of his diet for the purpose of improving his physical condition. Probably because of the constant presence of milk in his diet he had become suspicious of the bad effects of almost everything he ate. None of these suspected foods caused any trouble after milk was eliminated. On two occasions later the unintentional addition of milk products (frozen custard and swiss cheese) to his diet resulted in the recurrence to a marked degree of his previous symptoms.

There is another group of individuals whose symptoms probably come from intestinal irritation, in whom abdominal discomfort is the chief complaint. Their symptoms in general are similar to those of the group described above except that the bowel movements as a rule are not frequent. Some indeed of these individuals are constipated. The members of this group are usually older children and adults. The symptoms in certain cases have been repeatedly produced by giving to the patients foods to which they

are sensitive. In some instances there is dull pain, and in others sharp cramp-like pain. For example, one boy who had had attacks of cyclic vomiting for several years began to have abdominal discomfort later which prevented his sleeping and caused him trouble during most of the day from time to time. These latter symptoms had continued for three or four years when we first saw the boy and found him to be sensitive to chocolate and tomatoes. These two articles of food were removed from his diet following which there was complete relief from discomfort and a gain of 10 pounds in weight during the next month. While I have had no opportunity to prove the presence of spasm of the intestine in these cases, its occurrence is suggested by the fact that relief of symptoms sometimes results from the administration of atropine. There is much reason also to believe that the enterospasm, which is sometimes the only finding when the abdomen is explored surgically for appendicitis or intestinal obstruction, is of this nature. In some cases the severe pain followed some time later by vomiting might quite naturally suggest intestinal obstruction. Relief has been obtained in just this type of patient from the administration of atropine. I recognize the danger of assuming that symptoms like these have an allergic basis, and of course one should never make this assumption except as a last resort because of the great danger of missing other abdominal conditions with like symptoms which produce more serious consequences if the surgeon does not intervene. However, repeated attacks of this type not localized to the appendix region, associated with eating of certain foods and occurring in a patient with a personal or family history of allergy, should always be suggestive of an allergic etiology. In many instances the confirmation of positive skin tests may be obtained.

TREATMENT

After one finds the food or foods which are responsible for the allergic symptoms, treatment consists of removing the offending foods from the diet, or of modifying the food so that it will not cause symptoms, or of modifying the patient's response to the food. For example, if a patient is found to be sensitive to chocolate, it is not difficult to eliminate chocolate from the diet. Elimination of the offending food, if this is possible, is the most simple method of treatment and produces the most clear-cut results. However, if a small infant whose sole article of diet is milk is sensitive to that milk, then elimination is difficult. In this case it has been found that cow's milk that has been subjected to varying degrees of heat, such as dried milks or evaporated milk, may be taken without producing symptoms, when fresh milk cannot be tolerated. One of the factors in cow's milk to which children often become sensitive can be completely or partially destroyed by heat. If this modification of milk does not result in relief of symptoms it then becomes necessary, if the symptoms are severe enough, to change to some other food, such as goat milk or in some instances to soy bean preparations.

In older children where there is sensitiveness to several foods, and elimi-

nation would unduly restrict the diet, the patient's response to these foods usually can be modified through a process of what one may call desensitization. Patients themselves have a tendency to carry out this desensitization through repeatedly taking the foods to which they are sensitive, provided they do not take enough to produce severe symptoms. This is what the layman calls "out-growing" the condition. Desensitization to a food can be carried out through starting the patient on infinitesimally small amounts of the food by mouth and gradually increasing the amount. One must go slowly enough to avoid the production of symptoms if possible. This requires a great deal of patience, but we have successfully desensitized a number of infants to egg in this manner. The same principle is used in a more rapid desensitization to one or more foods by subcutaneous injections, beginning with very weak dilutions of extracts of the foods and gradually increasing the amount. One should begin with an amount sufficiently small so as to be sure that no demonstrable reaction occurs. We often begin with as weak a dilution as 1-1,000,000, or even less if the sensitiveness is severe. In this way we have successfully desensitized a number of children to foods to which they are sensitive, or at least have made it possible for them to take these foods without any discomfort—foods, the ingestion of which previously produced severe symptoms.

The above methods not infrequently are attended by discouraging results. Failures in many instances may be due to lack of patience, or may be explained by the fact that treatment has not included all of the foods which are contributing to the symptoms.

I am well aware of the fact that all of this is quite familiar to those working especially in the field of allergy, but the discussion seemed justified because of the fact that we continue to see large numbers of patients belonging to this group whose symptoms have received abundant unsuccessful treatment without any thought having been given to allergy as the probable etiologic factor.

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ABSCESS OF THE AORTA *

A CASE WITH PERFORATION WITHOUT ANEURYSM

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PURULENT lesions of the aorta are not frequent. Oetiker¹⁹ in 1924 found 81 cases in the literature to which she added five observed in Askanazy's institute. Auerbach¹ in a recent publication brought the cases up to a total of 133; this does not include cases of carcinomatous or tuberculous origin. According to the latter author, in 42 of these cases rupture of the aorta occurred, but in only 12 cases did this happen without the preceding formation of an aneurysm. Aneurysm occurred at the site of the lesion in a total of 56 cases. The case to be presented here would have to be added to the small group of 12 cases in which a pyogenic lesion of the aorta caused rupture without the formation of a localized dilatation.

These 12 cases were reported by 10 authors all of whose reports appeared between 1901 and 1931. They are, in chronological order: Kahliden,¹⁰ Witte,³¹ Scheuer,²⁴ Cooper,⁴ Luzzato,¹⁴ Schlagenhauer²⁵ (3 cases), Hanser,⁸ Stübler,²⁹ Desclin,⁵ and Levinson.¹² Pyogenic lesions of the aortic wall have been known for a long time.† The oldest detailed description must apparently be credited to Spengler,²⁸ who found, in a man 38 years of age, a small abscess in the media, just above the valve; this patient had died of a pyemia following tonsillitis.

An infectious process in the aortic wall may obviously enter from the lumen, through the vasa vasorum, or by direct contact from neighboring tissues. A frequent mechanism of origin is that by direct contact from infectious lesions in the aortic valves. Nauwerck and Eyrich¹⁸ drew attention to the existence of a primary verrucous aortitis; that is, one which occurs in the absence of valvular lesions. In a considerable number of the cases reported in the literature, the mode of entrance into the aorta is not mentioned or could not be reconstructed. Auerbach, who is the last to have made a careful analysis of the available cases, concludes that in the 41 cases in which pertinent data are at hand, the infection entered through the intima in 15, through the vasa vasorum in 14 and from adjoining tissue in 12. Oetiker ascribes 25 cases to contact from adjoining tissue, 12 to direct contact, and 47 to hematogenous metastasis—13 of these latter through emboli in the vasa vasorum and 34 through infection from the lumen. In the last

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† According to Spengler (1852), Rokitsansky quotes an observation by Andral who described a case with about half a dozen hazel-nut sized abscesses below the intima of the aorta; but Rokitsansky—still according to Spengler—doubted the correctness of Andral's observation. In 1856, Rokitsansky²¹ discusses (without the above reference to Andral) purulent arteriitis leading to aneurysm and terminating in rupture or pyemia.

34 reported cases, the infectious focus was superimposed in 22 cases on other aortic lesions, such as arteriosclerosis, lipiodosis of the intima, aortitis fibrosa or stenosis. In only three of these cases was the aorta reported to be normal with the exception of the purulent foci; in nine cases no mention was made of the condition of the aorta. Saphir and Cooper,²³ and Hausbrandt⁹ have reported cases in which pyogenic foci were superimposed on syphilitic aortitis.

The primary portal of entry is demonstrable in a minority of cases. This is obviously due to the fact that the primary focus may have healed completely long before the aortic lesion manifests itself; furthermore the primary focus may be rather insignificant in size and its site be difficult of detection. Purulent foci of many kinds may be the primary source of aortic infection; the following have been cited: tonsillitis (Spengler, Hausbrandt), traumatic phlegmonous foci (Scheuer, Koritschoner,¹¹ Edenhuizen,⁶) inguinal bubo (Foà⁷), rheumatic disease (Kahlden, Witte, McCrae¹⁶), endocarditis (Auerbach), salpingitis (Schmorl²⁶), mediastinal abscess (Roesner,²² Oliver,²⁰ Desclin), sepsis lenta (Siegmond²⁷), furunculosis (Buchaly³), pericarditis (Stübler, Maresch¹⁵), gonorrhea (Lindau¹³), chronic cystitis (Stumpf,³⁰ Auerbach), puerperal sepsis (Hanser), scarlet fever (Awdejeff²), vertebral caries (Schlagenhauser), erysipelas (Schlagenhauser), pulmonary infection (Luzzato). This list is incomplete and is included only in order to give an idea of the unlimited variety of lesions that may be the cause of purulent changes in the aorta.

A similar variety exists in regard to the offending microorganisms. According to Auerbach, microorganisms have been found in 70 cases; they were most frequently streptococci (in 26 cases), pneumococci (in 12), staphylococci (in 8), gonococci (in 2), "micrococci" (in 2), influenza bacilli (in 1) and anthrax bacilli (diagnosed on morphological grounds only (Oliver)) (in 1). Edenhuizen and v. Zalka³² and others have reported tuberculous lesions of the aorta.

In 99 cases the localization of the process is mentioned, as follows: ascending portion of the aorta, 70; arch, five; descending thoracic, eight; abdominal, 13; multiple localization in three.

In the 12 cases of purulent aortitis in which rupture occurred without aneurysm, the localization of the lesions was as follows: ascending portion, five (Scheuer, Kahlden, Stübler, Luzzato, Levinson); descending portion, four (Hanser, Witte, Desclin, Cooper); abdominal portion, three (Schlagenhauser). Perforation occurred into the pleural cavity in three cases (Scheuer, Luzzato, Cooper), into the lung in one (Hanser), into the pericardium in four (Kahlden, Stübler, Luzzato, Cooper), into the retroperitoneal space in three (Schlagenhauser), into the bronchial tree, that is the left main bronchus, in one (Witte). In Desclin's case the rupture occurred into an abscess between the aorta and pulmonary artery so that no bleeding took place. Pathological data throwing light on the probable mode of spread of the infection in these 12 cases may be outlined as follows:

Tonsillitis the probable primary focus (Levinson)	1 case
Phlegmonous inflammation of left foot, pulmonary infarction, involvement of aortic intima (Scheuer)	1 case
Puerperal infection from a recto-vaginal fistula, embolic pulmonary abscess, involvement of aortic intima (Hanser)	1 case
Rheumatic fever, fibrinous pericarditis, spread from pericardium into media of the aorta (Witte, Kahlden)	2 cases
Caries of lowest thoracic and first lumbar vertebrae, involvement of aortic intima (Schlagenhauser)	1 case
Erysipelas of left leg with probable embolism into aortic wall (Schlagenhauser) ..	1 case
Abscess in Douglas' space following a recent trauma, involvement of the aortic intima at the bifurcation (Schlagenhauser)	1 case
Pericarditis, hematogenous spread into the aorta (Stübler)	1 case
Abscess, origin unknown, between aorta and pulmonary artery, involvement of aorta (Desclin)	1 case
Chronic pulmonary infection with carnification, involvement of aortic wall (Luzzato)	1 case
Influenza one year before death, no purulent lesions found except ulcers in aortic wall (Cooper)	1 case

In all but Desclin's case, hemorrhage from the aorta was the cause of sudden death. In Desclin's case (Case V in his paper), the rupture of the aorta had occurred a considerable time before death. The immediate cause of death was massive hemopericardium in four cases (in one of these combined with hemothorax); massive hemorrhage into the retroperitoneal space in three; hemothorax alone in one; massive hemoptysis in two; and copious bleeding into the lung in one.

In practically all of these cases, clinical data are very scanty or lacking altogether. The symptomatology depends on the nature of the primary disease and on the localization of the aortic lesion. The impression is gained that localized pain may or may not be present, and that it is dependent not on the pyogenic lesion per se, but on effects of pressure and on associated pathological changes, such, for example, as pericarditis. Whenever symptoms, such as pain or dyspnea, are mentioned they may be adequately explained by associated lesions. Cooper mentions in his case severe pain in the left hypochondrium and the upper dorsal region, and delayed passage of food through the esophagus. In cases with aneurysm, pain is much more frequently mentioned.

In a number of the papers quoted above, detailed descriptions are presented of the histological changes in purulent aortitis. In general, they are essentially the same changes as in purulent inflammation in other tissues. Both Levinson and Auerbach emphasize the necrotizing processes in the media, that is particularly in the elastic elements. These two authors and Desclin point out that the exudate cells in the adventitia are predominantly polymorphonuclear cells, while those in media and intima are chiefly mononuclear. Certain structural details of the lesions provide the criteria for a reconstruction of the pathway of the infectious process.

CASE REPORT

G. H. C., a University professor, 59 years old, came to the office on April 10, 1931, complaining of a severe cold, with chills, fever, cough and pain in the chest.

His father, an exceptionally healthy man, had died at the age of 90. His mother

died at 68 of apoplexy. A brother and a sister had diabetes, and a paternal aunt and a sister had died of carcinoma.

The patient had a severe attack of "croup" when one year old, and subsequently up to the age of 42 several attacks of sore throat which he thought were diphtheria, although he was never treated with antitoxin. He had an attack of jaundice at seven, whooping cough at eight, measles at 22, and mumps at 25. Five years before, when 54, all his teeth were extracted on account of pyorrhea.

He had led a very healthy life, denied venereal disease, and had never used alcohol or narcotic drugs. He had smoked moderately until two years before. He had never married. For the past 20 years, working at his profession of teaching, he had never missed any time from work on account of illness.

When 28 he had an attack of "grippe." Two years before, when 57, he had an attack of "influenza" with severe cough and hoarseness. He did not know whether he had fever, but worked throughout the attack which lasted about a week. During this illness he also had conjunctivitis which was epidemic at the time.

Since then, he had a few acute head colds and a tendency to stuffiness and scabby secretions in his nose. He had no headaches. Also, since this attack he had a few chest colds, always with much cough but with difficulty in raising any sputum. He did not have chronic cough, hemoptysis or asthma.

For the past few months he had noticed polydipsia and accompanying polyuria.

About ten days before he developed a head cold followed by cough and probably fever. He had felt badly, not eaten well, and had one vomiting attack a week before. Two days before, feeling feverish, he treated this by getting into a tub of cold water. Since then he had pain of a pleuritic character in the left chest, felt more feverish, and his cough was tighter.

The following notes were made on the physical examination at the first visit, and on the laboratory findings and roentgen-ray films a few days later:

PHYSICAL EXAMINATION: Wt. 161. Pulse 92. Temp. 101.4. B.P. 130-88. Tired appearing, elderly man, well nourished. Lips slightly cyanotic.

Eyes: Sclerae slightly icteroid. Pupils equal and regular, react sluggishly to light.

Upper respiratory tract: No tenderness over frontal sinuses or antra. Mucous membrane of nose is very dry and in left nostril there is a mass of bloody scabs. Pharynx; pillars and posterior palate show a bright red injection. Right ear drum normal, left a little injected in the upper half.

Mouth: The teeth all absent. Tongue covered with brownish coat.

Lymph-nodes: Not enlarged.

Thyroid: Not enlarged.

Chest: Well formed. Expansion fair, and apparently equal.

Heart: Apex beat in fifth intercostal space inside mid-clavicular line. Percussion outline not enlarged. Sounds normal.

Lungs: Percussion note good. Breath sounds rather harsh throughout. At the right base posteriorly a few medium râles are heard, not changed by cough. Fluoroscopy of chest: Heart is of broad shape. Mediastinal shadow broad. Posterior space clear. Diaphragm appears normal. No definite abnormalities in lung fields.

Abdomen: Full. No rigidity, tenderness or masses. Liver and spleen not felt. Left inguinal ring is large and on coughing a small hernia is felt.

External genitalia: Normal.

Extremities: Joints clear. Fingers not clubbed.

Reflexes: Knee jerks obtained with difficulty, only after reinforcement. Romberg negative.

LABORATORY FINDINGS: 4-13-31.

Urine: Voided specimen: Acid. S.G. 1025. Albumin: ++. Sugar: 2 per cent. Acetone: positive. Indican: trace. Bile: negative. Microscopical: very rare white blood cells, no red blood cells, 4 hyaline and 6 finely granular casts per low power field.

Blood: Red blood cells 4,900,000; hemoglobin 90; white blood cells 23,000. Differential: polymorphonuclears 94 per cent, small lymphocytes 2 per cent, large lymphocytes 2 per cent, transitional 2 per cent.

Blood sugar: 156 mg.

Non-protein-nitrogen: 27.6 mg.

Wassermann: Negative.

Sputum: 30 c.c., mucoid, blood streaked, no tubercle bacilli, many streptococci, staphylococci and pneumococci.

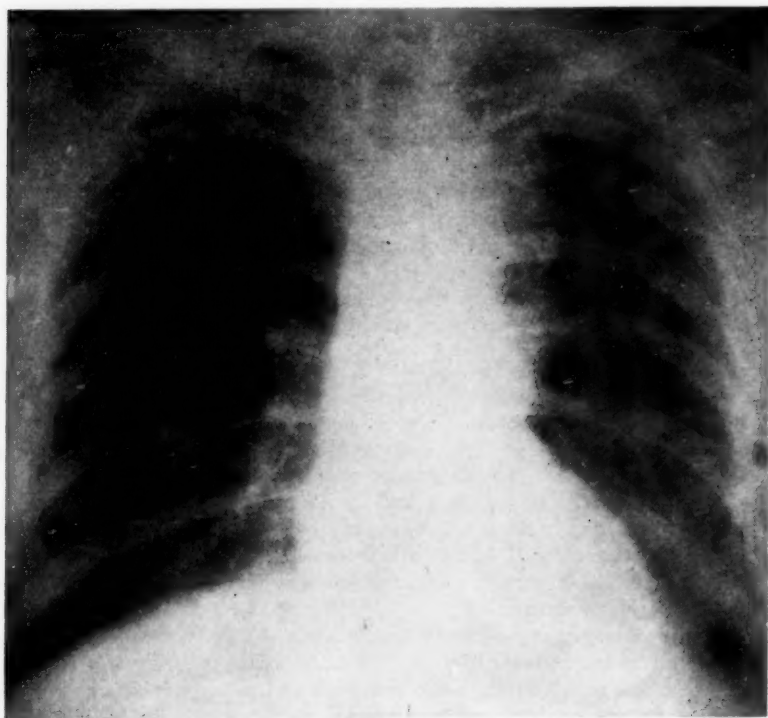


FIG. 1. Roentgenogram of 4-13-31, showing the shadow adjoining the left upper mediastinum. (Details in the text.)

ROENTGENOLOGICAL FINDINGS:

Sinuses P.A. (4-13-31): There is a little erosion of the upper walls of the frontals, suggesting an old frontal infection. The antra are clear. The septum is deflected a little to the right.

Chest (4-13-31): There is a marked density in the upper left mediastinum extending from about the fourth rib posteriorly down to the eighth, with its lateral margin 7.0 cm. from the midline. The lateral margin is fuzzy in outline. Through the density there is a moderate amount of honey-combing. The pleura around the left lung is thickened. The bony thorax is normal. There is a little thickening of the pleura on the right. (See figure 1.)

Chest (Bedside 4-21-31): No appreciable change since the previous film was taken.

Lateral chest (4-24-31): The lung fields are not clear because of motion. The thickened pleura can be traced along the anterior wall. There is very marked bridging between five of the lower thoracic vertebrae.

The patient was put to bed at his home. On the morning of the second day following he had a chill and a rise of temperature. He was seen in the afternoon at home, at which time he had a tight cough, pain in the left chest near the sternum, a temperature of 103°, pulse 92, and respirations 36. There was an impairment of resonance, harsh breathing and moist râles at the right base posteriorly, but no abnormal signs were found in the left chest. He was thought to have a pneumonia at the right base and was sent to a hospital.

He was put on strict bed rest, and, as soon as the glycosuria and acetone were reported by the laboratory, a restricted carbohydrate and low fat diet with insulin was ordered. He had no medication except tincture of digitalis, 60 minims a day, for about a week.

During his first week in the hospital the respiratory symptoms improved and the glycosuria and acidosis disappeared. His maximum daily temperature became 100.2°, his pulse 72, and respiration 30. Following this improvement, however, he had a sudden exacerbation with a pulse of 104 and respirations of 40, and on the next day a rise of temperature to 101.6°, but without other change in symptoms or chest signs.

On the tenth day after admission to the hospital he developed a conjunctivitis in the left and two days later in the right eye, which subsided after a few days.

On the twelfth day he passed a black tarry stool with a few streaks of bright blood, but had no accompanying nausea, vomiting, pain in the abdomen or other symptoms.

On the thirteenth day he began to have pain in the left shoulder which became severe. There were no objective signs of inflammation. Three days later the proximal phalangeal joint of the left index finger became swollen, painful and red, and the next day the corresponding joint of the left ring finger was similarly involved.

By the end of the third week in the hospital the temperature had gradually decreased to a daily maximum of 99.8°. The pulse and respirations still remained high, however: up to about 110 and 32 respectively. He still had a slight dry cough and sometimes on deep breathing a little pain just to the left of the sternum. The impairment of resonance and râles persisted at the right base, but the breath sounds had become much more nearly normal. By careful percussion an area of slight impairment of resonance extending about one finger's breadth to the left of the sternal border in the first and second interspaces could be made out, but there were no changes in breath sounds or râles over the left lung. The blood pressure in both arms had remained about 135 systolic and 90 diastolic. No abnormal pulsations of the chest wall, no thrills, no tracheal tug and no delay in either radial pulse could be detected. The eye grounds had been examined and had appeared normal. The glycosuria had been easily controlled by diet and insulin.

On the morning of May 3, about five weeks after the onset of illness, and three weeks after entering the hospital, the patient felt and appeared unusually well. At 11:30 a.m. while lying quietly in bed he began to cough up bright blood in large quantities. This continued and he bled to death within a half hour.

CLINICAL DIAGNOSIS

Mediastinal tumor (abscess, neoplasm, aneurysm?) with rupture either of the aorta or of a pulmonary vessel.

Acute upper respiratory tract infection.

Bronchopneumonia in the right lower lobe.

Acute conjunctivitis.
Acute polyarthritis.
Diabetes mellitus.
Atrophic rhinitis.
Osteo-arthritis of dorsal vertebrae.

DISCUSSION OF CLINICAL FEATURES

When this patient presented himself his picture was definitely that of an acute respiratory infection; rhinitis, pharyngitis, and bronchitis. The subsequent appearance of definite physical signs at the right base pointed to a pneumonic process. Roentgen-ray examination, however, showed only minimal involvement in this area but disclosed a massive lesion of some sort in or adjacent to the left border of the upper mediastinum. In the course of the disease, after the acute infection had subsided, it became apparent that this was the lesion of greatest significance and finally it seemed probable that death by rupture of a blood vessel was due to it.

As to the nature of this mass no definite diagnosis was made clinically. Abscess, neoplasm, and aortic aneurysm were considered.

The termination with rupture and profuse bleeding was highly suggestive of aneurysm. The roentgen-ray appearance, however, was not that of aortic aneurysm. The shadow was irregular in density and outline instead of showing a characteristic homogeneous sharp-edged appearance. None of the classical symptoms or signs of aneurysm were present. There was no history or evidence of syphilis, and the blood Wassermann was negative.

Mediastinal neoplasm might cause the roentgen-ray picture here seen. In fact the roentgenological appearance seemed most consistent with such a diagnosis, and the patient's age was in keeping.

Abscess of the mediastinum would explain the persistence of the symptoms, fever, leukocytosis, pain and the complicating conjunctivitis and polyarthritis and perhaps, though not typically, the roentgen-ray picture. The usual causes of mediastinal abscess, extension from a retro-pharyngeal or peritonsillar abscess, rupture of a caseous lymph node, or trauma were absent. Metastatic mediastinal abscesses from focal infection elsewhere in the body are rare. Mediastinal abscesses by extension from an influenzal pneumonia were fairly frequent during the epidemic of 1918 (McLester¹⁷), but such an etiology could not apply to the present case. The occurrence of frequent head and chest colds since the acute respiratory infection, similar to the present one which the patient had two years ago, suggested the possibility of a focal infection of the nasal sinuses, or possibly a bronchiectasis, from which one of the rare metastatic mediastinal abscesses might have originated.

We considered these possibilities without being able to make a definite diagnosis. The true pathology of the lesion shown in the roentgen-ray films was disclosed only by the autopsy.

PATHOLOGICAL FINDINGS

The autopsy was performed six and a half hours after death. The pathological-anatomical diagnosis was: Abscess of the arch of the aorta with rupture into the aortic lumen and into the left upper lobe. Sanguinous imbibition of the medial portion of the left upper pulmonary lobe. Atheromatosis of the aorta, of its larger branches and of the coronary arteries. Incipient cirrhosis of the liver. Multiple varices in the mucosa of the jejunum. Osteo-arthritis of the thoracic vertebrae with complete ankylosis.

A detailed description of the pertinent findings follows:

At the peripheral end of the aortic arch, the aorta is adherent to the left upper pulmonary lobe. In this region, there is a mass of the shape of a half sphere which, with its broad base, is firmly attached to the aorta, while its dome is attached to the

left upper lobe; it measures about 5 cm. in its greatest diameter. The medial portion of the upper lobe is soggy and non-crepitant. After the aorta is opened on its anterior surface, a round hole is seen in the intima at the location of the mass between aorta and upper lobe. This hole has well defined, slightly depressed borders, and measures



FIG. 2. Section through intima and part of the media near the point of perforation, showing chronic pyogenic foci invading and destroying the elastic fibers. Weigert's elastica stain; magnification approximately 100 \times .

1.5 cm. in largest diameter. It leads into a cavum, extending through the aortic wall to a depth of about 1 cm. This cavum contains some dark blood clots. A section through the aortic wall and the left upper lobe through the center of the cavum, shows that the aortic wall reaches, without break and without thickening, to the margin of the hole and that the tissue adjacent to the aorta is markedly thickened, beginning 2 cm. above the hole and extending 5 cm. below the hole. In this whole extent, the aorta is adherent to the lung through flat thick adhesions in which a white firm layer, 1 to 3 mm. thick is seen, parallel with the aortic wall. The thickened tissue extends in the form of a flat arch across the cavum, but it is perforated at the point

of greatest elevation forming an open tract leading from the aortic lumen through the cavum into the subpleural tissue of the left upper lobe. Water instilled into the left upper bronchus spurts out freely from a small bronchus directly adjacent to the pleural perforation. The pulmonary tissue in this region is dark red, apparently devoid of air and friable; some dark blood is easily pressed out from the parenchyma.

The intima of the entire aorta shows moderate atheromatosis without calcification and without ulceration. The cardiac valves show no gross changes, and there is no dilatation of the aorta. The other organs do not reveal any pertinent findings.

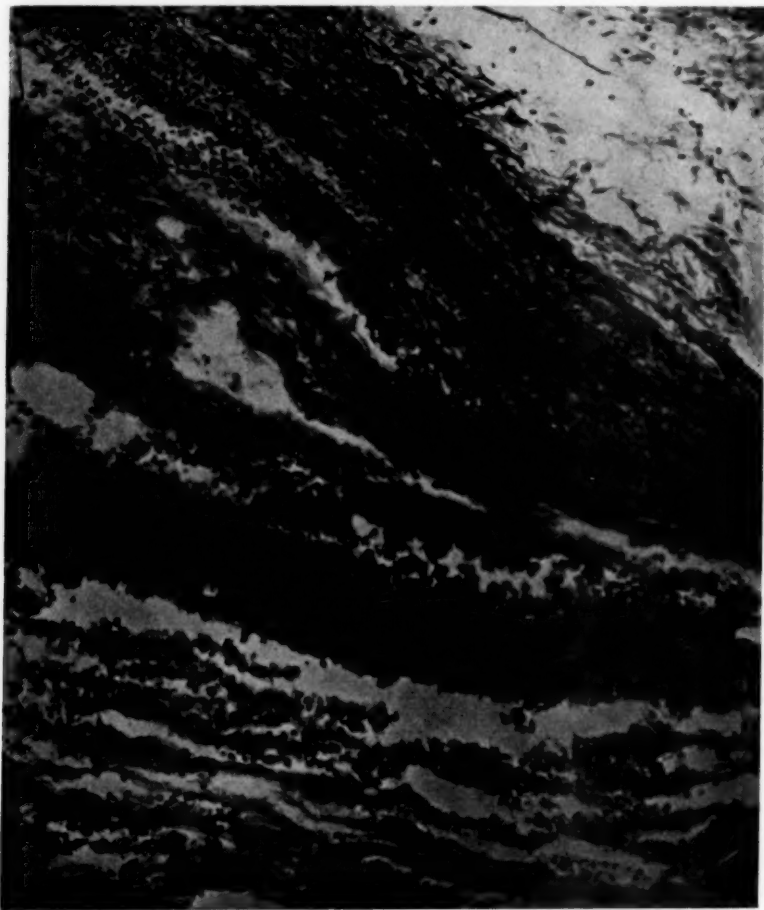


FIG. 3. Section through media and adventitia, showing massive pyogenic foci with complete destruction of elastic fibers. Weigert's elastica stain; magnification approximately 150 \times .

Histological Findings. Sections through the aorta, adjoining the perforation, show the entire thickness of the aorta irregularly infiltrated with cells. There are dense accumulations of cells surrounding small areas of granular debris, rather rich in amorphous nuclear material; in such areas in the adventitial and median layers, the normal structures are completely effaced. In other areas there are dense cellular infiltrations without necrosis, and in still other ones, smaller accumulations of cells are moulded between separated elastic lamellae. (See figures 2 and 3.) The predominant

cells composing this exudate are fairly large mononuclear histiocytes; there are relatively few lymphocytes and plasma cells, and few polymorphonuclear cells. (See figure 4.) In the adventitial region, and bordering on the pleura, are more or less parallel strands of fibrous tissue which, however, are interspersed with exudate cells as described above. The elastic fibers of the aorta are more or less separated by cellular exudate, and destroyed in regions of massive infiltration or necrosis. (See figures

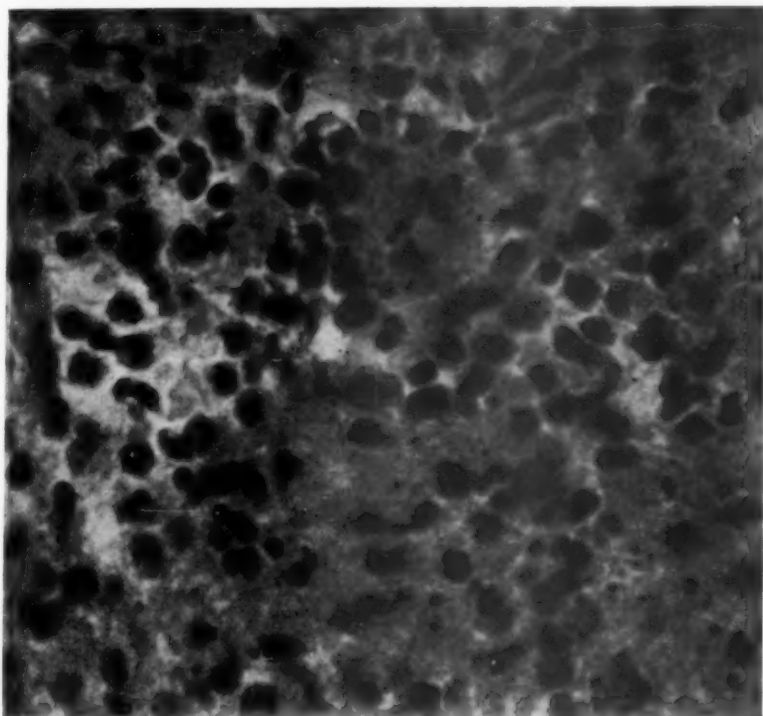


FIG. 4. Section through a medial abscess, to show the type of cells present. Hematoxylin-Eosin stain; magnification approximately 500 \times .

2 and 3.) Sections taken at different levels show that more of the deeper elastic fibers are destroyed, and that the most superficial layers are absent only near the center of the lesions. This suggests that the destruction advanced from the adventitia towards the intima, and the cellular infiltrations, too, indicate in their distribution the same order of development. Near the perforation, cellular infiltrations and necrosis undermine for a distance of two to three millimeters well preserved elastic fibers, suggesting that the process advanced in the outer medial layer centrifugally before perforation occurred. The elastic membrane of the pleura is destroyed in part and the adjoining pulmonary tissue shows slight cellular infiltration of the same character as the aortic wall. In addition there is some compression of the parenchyma, slight perivascular peribronchial and interalveolar fibrosis, and many alveoli contain pale staining red cells.

Gram stains failed to reveal any microorganisms in the foci either in aorta or lung. No attempts were made to culture organisms from the lesion.

Sections of the aorta at various levels, distant from the abscess, show intimal atheromatosis, but no pyogenic lesions.

Histological studies of the other organs revealed no findings of significance.

COMMENT

The patient died by exsanguination caused by the rupture of an abscess of the aortic wall into the aortic lumen and into the lung. In attempting to correlate the autopsy findings with the clinical course, it must be pointed out that the abscess is undoubtedly of longer duration than the patient's last acute illness. The relative chronicity of the abscess is indicated by the massive fibrosis on its pleural surface and by the fibrosis in the adjoining pulmonary tissue. It is questionable whether the rarity of polymorphonuclear leukocytes in the exudate can be used as an argument in the same direction, since other workers, as mentioned, have observed a similar preponderance of mononuclear exudate cells in the media of the aorta.

As to the location of the primary focus it has already been suggested in the discussion of the clinical features that the patient may have had a chronic focal infection in the respiratory tract. The appearance of the nasal mucous membrane suggested a chronic with a superimposed acute condition, and the roentgen-ray films of the nasal sinuses were in line with this. It is possible that a small metastatic abscess in the adventitia of the aorta, in the adjacent mediastinal tissues, or possibly in the lung itself, may have resulted from such a chronic focus. On this hypothesis the sequence of events would have been an acute infection, probably the one two years previous, a chronic focus following this, a later metastatic abscess in or adjacent to the aorta, with an exacerbation of this abscess by the acute respiratory infection preceding death, and its final rupture. In this exacerbation the complicating diabetes may also have been a factor.

Dr. R. H. Jaffé, in a personal communication, states that he has seen in influenza, purulent lymphangitis in the adventitia of the aorta. He suggests that the lesion presented here may have started as such a lymphangitis.

If such were the etiology in the present case, then the abscess may have originated during the attack of so-called influenza two years previously, doing away with the necessity of supposing any subsequent focal infection as its source. There is, however, no evidence that this attack was a true influenza.

These are mere conjectures, of course, and it is impossible to state definitely what was the primary source of the aortic abscess. In any event, it is obvious that the purulent aortic lesion did neither develop from the lumen, nor from infectious emboli in the vasa vasorum, but that it started either in the adventitia proper, or in tissue between the adventitia and the subpleural pulmonary parenchyma.

The last febrile illness of our patient, although apparently not caused by the aortic abscess, probably resulted in an exacerbation of that lesion; this caused the chronic abscess to perforate. It is likely that for some time preceding death, a seepage of blood from the aorta into the lung occurred, since the red cells in the lung were poorly stained, partly laked cells which could not have originated from the terminal hemoptysis. This sanguinous imbibition of the pulmonary tissue must be the cause of the roentgenological

shadow in the upper left pulmonic field; the abscess per se is far too small to be held responsible for this shadow.

It would appear quite possible that the acute arthritic symptoms were caused by hematogenous propagation of the abscess contents.

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THE PARENTERAL ADMINISTRATION OF MAGNESIUM SULPHATE IN HYPERTENSION*

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ALTHOUGH magnesium is an important component of all tissues, its proper place in the various processes in the body is but vaguely understood. Outside of the skeletal system where it is found in small quantities, it occurs in all the other organs of the body, at times in even greater quantities than calcium. By the method of Denis,¹ the blood stream contains quantities of magnesium ranging from 1.6 to 3.5 mg. per 100 c.c. Mathews² found it to be excreted in the urine to the amount of 1 gram per day as magnesium phosphate.

A number of interesting and important papers have appeared at intervals on the physiological effect of magnesium. Loeb³ in 1902, called attention to the depressant effect of magnesium and demonstrated its action in reducing muscular twitchings. Its ability to stop the tremors in tetany in cases of diminished calcium is clearly demonstrated. Beginning in 1908, Meltzer and Auer⁴ published a series of papers based on a number of experiments and again called attention to this unique action of magnesium. They showed that it has an anesthetic type of depressant action on animals when applied to the nerve trunk or when injected intravenously or subdurally. They demonstrated a marked effect on the involuntary musculature and on the various elements of the nervous apparatus.

It is the belief of a number of clinicians that magnesium salts are toxic if introduced into the circulation. Meyer and Gottlieb⁵ pointed out that only a few decigrams given at one time are sufficient to paralyze the respiratory center. Meltzer and Auer⁶ showed, on the other hand, that the toxicity of magnesium salts does not depend alone on the quantity of salt injected but also upon the speed with which the injection is given. They considered that 0.1 to 0.2 gm. of the salt per kilo rabbit, is capable of completely abolishing the respiration and profoundly affecting the blood pressure when administered intravenously by rapid injection. On the other hand, a rabbit will apparently stand even as much as 1 gm. per kilo if the intravenous injection is given with sufficient slowness. According to Solis-Cohen and Githens,⁷ if dogs are given M/1 solution at a rate of 1 c.c. per minute, the fatal dose per kilo is 2.86 c.c. corresponding to 0.224 gm. of the dry sulphate. In rabbits, the respiration is stopped and the animal killed by 0.05 gm. per kilo injected in 20 seconds but not by 0.25 gm. in 12 minutes or by 0.75 gm. in 60 minutes. They further assert that as much as 500 c.c. of a 2 per cent solution of magnesium sulphate may be

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given intravenously in man provided it is given slowly at the rate of about 10 c.c. per minute.

Stander,⁸ in an effort to establish the toxicity level of magnesium sulphate experimentally, showed that magnesium sulphate in total doses ranging from 0.05 to 0.49 gm. per kilo of body weight administered to dogs either intramuscularly or intravenously in 10 or 25 per cent solution, did not produce any marked changes in the blood on chemical examination but did produce histologic changes in the liver and kidneys in the form of moderate necrosis in the central part of the liver lobule and moderate degeneration in the convoluted tubules of the kidneys. He further stated, however, that in his opinion the non-toxic dose for human beings should not exceed 0.1 gm. per kilo of body weight.

The antagonistic action of magnesium to calcium which increases the tone of the smooth musculature was observed by Meltzer and Auer.⁴ This interesting inter-relationship was further demonstrated by Mendel and Benedict⁹ in the increased elimination of calcium in the urine upon the intravenous injection of magnesium. That the body has a great tolerance for magnesium was shown by Joseph and Meltzer¹⁰ who reported the lethal dose in dogs as .223 gm. of magnesium chloride per kilo of body weight. Matthews and Austin¹¹ in 1926, showed that .223 to .228 gm. of hydrated magnesium sulphate ($\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$) per kilo is the fatal dose for the dog with a normal blood calcium. They further proved that this tolerance can be increased by the injection of calcium salts. During the same year, Woitaschewski¹² also called attention to its depressant effect. Matthews and Brooks¹³ in 1910, using magnesium sulphate, reported a drop in blood pressure in experimental animals. Consequently, in view of the observations of others in animals, it seemed desirable for us to demonstrate the effect of magnesium sulphate in the treatment of hypertension in man.

The application of a drug in the treatment of human ailments involves entirely different factors from those which are found in the experimental animal. In the first place, in the human subject with hypertension, we are dealing with an organism which is in a pathological state. Furthermore, the pathological state which presents itself with the symptom of hypertension is by no means a definite entity, dependent upon the same causes in each case. The pathogenesis of hypertension is still an unsolved question. We merely know that the varied factors which are likely to elicit hypertension include: toxic states either of infectious or endogenous origin; metabolic or definitely endocrine disturbances; and finally, abnormal conditions of the central nervous system. Psychic factors also play a considerable rôle. It is frequently impossible to determine which of these factors is involved; moreover, a combination of several of these factors is not uncommon. Magnesium is a chemical capable of counteracting many of the forces enumerated in the complex pathogenesis of hypertension. Among these, two are most conspicuous—its ability to relax the smooth musculature and its sedative effect upon the nervous system.

Although in view of experiments in animals by others one can safely predict that the injection of magnesium will reduce the blood pressure in these experimental animals, this cannot be predicted with certainty in the human body in a state of hypertension because other factors may be present to counteract this action. In our experiments during the past year at the Kings County Hospital, in a series of 50 consecutive cases of hypertension, we found the depressing effect of magnesium upon the nervous state of the patient to be of value. This, surely, is not a factor encountered in the experimental animal.

Twenty-one cases of the series were hospital patients presenting a multiplicity of symptoms such as severe and persistent headache, insomnia, vertigo, hot flashes, buzzing in the ears and throbbing in the head. In many of our cases, these symptoms of hypertension were severe. Some of the patients showed, in addition to these symptoms, marked sclerosis of the peripheral blood vessels. Although no relief of these blood vessel changes could be expected from any treatment, these patients were not excluded from our series, in order to test the value of the procedure in an unselected series. The blood pressures in all of these cases were studied for a period of from one to several weeks before treatment with magnesium was attempted. This was done to study possible fluctuations in pressure with the patient at rest.

Twenty-nine of our series were Out-Patient Department cases who were taken off all medication for a period of seven days for the purpose of observation before the study of magnesium was started. Eighty per cent of these patients presented one or more of the symptoms of hypertension to a marked degree.

Fifteen of our patients showed evidence of nephritis; 32 showed atheromatous changes in the aorta—that is, widening of the aorta with a loud systolic murmur over the aortic area transmitted to the vessels of the neck. Thirty-five patients showed peripheral changes in the radial arteries, such as thickening and calcification. Retinal changes were observed in 24 of these individuals.

In this study, we were fully conscious of the difficulty of making definite observations and drawing definite conclusions when dealing with such a labile factor as blood pressure. In order to reduce the factors of error, we attempted to standardize our procedures. We therefore adopted the following routine: 1. Blood pressure readings were taken thrice daily for a period of a week on all hospital cases. On the Out-Patient Department cases, one single reading was taken each morning at the same hour, for a period of a week. 2. All injections were given at a definite hour in the morning. Ambulatory cases were rested in the supine position for a half hour before the injection was given, in a separate quiet room where all of our studies were made. 3. Blood pressure readings were made one, two and three hours after injection and every morning thereafter, at the same hour, for at least two weeks. 4. Three blood pressure readings were taken

at five minute intervals on all cases. The first reading was always discarded because we did not find it to be accurate; hence, we took the mean reading of the other two. It is needless to mention that the proper application of the cuff and a not too rapid inflation were carefully observed. All readings were taken by the same observer.

Preparation of Solution. In making this study, we used chemically pure, anhydrous magnesium sulphate (Mallinckrodt) in triple distilled water. A stock solution of 25 per cent by weight was prepared. All dilutions were made from this immediately before using, by adding warm, sterile, triple distilled water. We can say that in the first 10 cases of our study we used 1/10 gm. per kilo of body weight in the form of a 12½ per cent solution. We felt that this concentration was too great because of the marked subjective heat sensation in some of these patients. In our subsequent cases, we used a 2½ per cent solution injecting .035 gm. per kilo of body weight, an amount which is well below the toxic dose reported for animals by others. Aside from one case of syncope which we encountered in our initial 10 cases when we employed a more concentrated solution of magnesium, our patients experienced no untoward reactions. This case of syncope was promptly relieved by an injection of adrenalin.

Technic of Injection. A graduated salvasan cylinder was used. A length of rubber tubing ended in an adapter for a luer needle. The rubber tubing was interrupted at a point 12 inches from the needle by a petcock so that the flow could be interrupted at any time upon complaint of the patient of excessive body heat. A twenty gauge needle of two inch length seemed to be ideal. The level of the fluid in the cylinder was kept at approximately 18 inches above the anterior chest wall of the patient at all times. The solution was warmed to body heat and was delivered to the patient intermittently in accordance with the sensation of heat experienced by the patient. The rate of flow of the solution was approximately a half hour per 100 c.c. The patient remained at rest in bed for two hours after the injection. The ambulatory cases were then permitted to go home.

We studied our cases from two points of view: (1) the effect of magnesium sulphate on the blood pressure; (2) the effect of magnesium sulphate on the subjective symptoms of the patient. We believe that the study of the latter is even more important than the study of the effect on the tension. It is a known fact, as has been observed in a great number of our cases, that the symptoms presented by patients with hyperpiesia are not in direct proportion to the degree of hypertension. Many patients are observed who have had high tensions for extended periods of time and yet have been able to attend to their usual duties without symptoms. These patients do not appear for treatment unless through some accidental finding, as a health or an insurance examination, the elevated blood pressure is discovered. The majority of the cases, however, complain of definite and distressing symptoms; hence, the relief of these symptoms is as important a factor in the treatment of hypertension as is the reduction in pressure itself.

TABLE I

Effect of Parenteral Administration of Magnesium Sulphate on Systolic Blood Pressure

Case Number	Blood Press. before Injection	Average Drop in 1st 3 Hrs.	Drop 1 Day After	Drop 2 Days After	Drop 3 Days After	Drop 4 Days After	Drop 5 Days After	Drop 6 Days After	Drop 7 Days After	Average Drop in 1st Week	Average Drop in 2nd Week
1	180	33	20	30	40	20	40	20	20	28	20
2	230	59	60	40	60	40	35	40	40	47	40
3	220	58	30	40	50	52	55	45	55	48	73
4	230	27	50	52	48	45	46	50	60	47	40
5	190	15	20	30	40	30	25	15	30	25	38
6	198	40	18	24	26	28	30	30	30	28	30
7	240	23	28	16	20	20	22	24	26	23	28
8	162	28	+12	+20	+12	+10	+14	+18	+16	+12	+20
9	170	17	5	5	+5	10	12	10	10	7	10
10	200	23	15	10	15	15	10	35	30	19	25
11	230	40	42	30	50	35	20	0	5	28	62
12	195	20	5	31	50	15	40	25	40	28	45
13	180	15	10	6	25	10	+5	10	15	14	23
14	200	11	15	+10	+20	5	+20	+35	+15	+9	+3
15	220	10	40	20	20	25	20	25	25	23	25
16	185	11	47	55	43	40	35	15	20	33	25
17	215	0	+5	+10	+5	+5	+19	+15	+16	+9	+13
18	260	20	20	15	30	30	30	30	25	25	30
19	248	25	23	20	20	25	30	38	35	27	33
20	240	+30	5	65	50	70	75	80	85	50	65
21	235	3	40	45	35	30	35	35	35	32	35
22	190	25	25	25	30	22	26	25	25	25	33
23	180	20	20	20	12	27	24	26	30	22	42
24	184	26	24	20	19	20	12	22	24	21	24
25	235	61	55	43	40	35	40	20	17	39	14
26	226	31	51	50	45	45	46	45	41	44	51
27	245	35	65	60	60	65	55	51	55	56	58
28	176	21	31	31	30	26	28	28	28	28	31
29	224	39	40	39	46	45	50	45	40	43	34
30	205	20	25	21	25	28	20	20	26	23	27
31	208	44	48	40	45	43	40	38	40	42	45
32	225	45	43	35	35	40	40	35	30	38	30
33	260	40	+5	40	44	40	42	40	35	34	35
34	212	27	37	47	45	40	45	48	45	42	50
35	188	40	38	35	40	34	36	32	18	34	19
36	170	30	26	22	25	22	30	20	26	25	28
37	212	32	37	38	42	54	50	52	47	44	37
38	260	55	75	72	74	84	82	80	74	74	76
39	200	55	35	36	58	54	40	45	46	46	44
40	165	30	17	+5	+10	+9	+15	+15	+20	+3	+25
41	220	56	70	55	60	65	65	54	65	61	61
42	180	20	25	20	12	12	20	18	20	18	23
43	205	30	40	41	50	40	41	45	40	41	40
44	178	33	35	38	40	43	35	38	35	37	38
45	185	15	+7	+9	13	10	15	10	0	6	15
46	185	5	5	5	25	20	20	20	20	15	15
47	194	20	64	50	45	39	26	34	40	40	44
48	210	55	50	40	40	45	40	42	42	44	40
49	175	19	31	30	30	25	20	20	25	25	19
50	190	25	25	25	30	22	26	25	25	25	33

+ indicates rise instead of fall in blood pressure.

I. EFFECT OF MAGNESIUM SULPHATE ON THE BLOOD PRESSURE

(A) *Effect on Systolic Pressure.* From a summation of table 1, one finds that four cases showed an average rise ranging from three to 12 mm. of mercury during the first week; four cases showed an average rise of three to 25 mm. during the second week. Forty-six cases responded favorably with some fall of pressure. Eliminating all cases which did not show an average drop of 20 mm. of mercury during the first week, there were 25 cases which showed an average drop of 21 to 40 mm. and 15 cases with a fall more than 40 mm. during the first week.

There were 26 cases which showed an average fall of 21 to 40 mm. in the second week and 13 cases with a fall more than 40 mm. It will be noted that in the majority of cases, the fall in systolic pressure runs uniformly in the same cases during the two week period of study. In four cases (8, 14, 17 and 40) there was a fall in systolic pressure in the first three hours after injection, followed by a rise on the first or second day. This rise was sustained throughout the entire study. In one case (20), there was a marked rise of 30 mm. within the first three hours with a subsequent marked and persistent fall of practically twice the initial rise. In two cases (33 and 45) slight rises of five and nine mm. of mercury were noted within the first two days after injection with subsequent falls of 40 and 13 mm., respectively, which persisted throughout the study.

Table 2 illustrates the number of cases of the series with their respective falls in pressure on successive days of the study. The last column denotes the average fall during the second week of study. One readily recognizes

TABLE II
Summary of Effects of Magnesium Sulphate on Systolic Pressure

No. of Cases Showing	3 Hours After Injection	1 Day After	2 Days After	3 Days After	4 Days After	5 Days After	6 Days After	7 Days After	2nd Week After
No drop	1	0	0	0	0	0	1	1	0
Drop 1-10	3	5	4	0	4	1	3	2	1
Drop 11-20	13	8	6	8	6	9	9	7	6
Drop 21-30	13	9	9	10	13	11	10	15	12
Drop 31-40	10	11	14	8	10	12	10	10	14
Drop 41-50	2	6	6	14	7	7	8	5	6
Drop 51-60	6	3	4	4	3	2	3	3	2
Drop 61-70	1	3	1	0	3	1	0	1	3
Drop 71-80	0	1	1	1	0	1	2	1	2
Drop 81-85	0	0	0	0	1	1	0	1	0
Rise	1	4	5	5	3	5	4	4	4

from this table the relative uniformity in the number of cases showing a constant fall in the systolic pressure throughout the period of observation.

(B) *Effect on Diastolic Pressure.* From a summation of table 3, one

TABLE III

Effect of Parenteral Administration of Magnesium Sulphate on Diastolic Blood Pressure

Case Number	Blood Press. before Injection	Average Drop in 1st 3 Hrs.	Drop 1 Day After	Drop 2 Days After	Drop 3 Days After	Drop 4 Days After	Drop 5 Days After	Drop 6 Days After	Drop 7 Days After	Average Drop in 1st Week	Average Drop in 2nd Week
1	120	25	20	30	10	20	25	20	20	21	18
2	130	30	25	25	15	10	12	14	12	18	10
3	135	14	15	5	0	15	30	25	45	19	43
4	110	9	10	12	12	10	10	8	8	10	8
5	120	15	15	15	20	20	20	20	20	18	20
6	62	+24	+10	+14	+2	+8	2	+2	+2	+8	+2
7	130	10	2	+2	2	+2	+2	4	6	2	6
8	78	"	2	+6	4	6	12	10	8	5	6
9	100	12	0	0	5	0	0	4	0	3	4
10	140	5	20	0	10	20	10	20	20	13	20
11	120	0	0	0	10	10	10	0	+20	1	8
12	90	0	+5	2	+10	+5	+5	0	0	+4	+5
13	105	5	+5	+5	5	+15	+15	+5	15	+2	5
14	120	10	10	0	+10	+20	+30	+25	+5	+9	+4
15	120	+5	+5	0	+10	+10	+8	+10	+10	+7	+10
16	110	22	30	34	20	40	34	35	30	31	28
17	120	+10	10	+10	+10	+10	0	20	+8	+2	+10
18	150	20	20	0	0	24	0	10	10	11	10
19	125	15	13	10	10	10	8	5	5	10	8
20	140	0	5	30	30	30	20	30	30	21	25
21	130	+2	5	0	20	4	15	10	15	8	13
22	100	+5	0	0	+4	+5	+10	+10	+10	+6	+15
23	95	+6	5	5	13	7	14	12	11	8	11
24	118	3	+2	+6	+4	+2	+4	+2	0	+2	+1
25	130	27	15	12	10	12	10	10	8	13	5
26	116	18	1	8	11	14	16	13	11	12	12
27	130	0	20	15	15	15	18	15	20	15	18
28	108	3	16	10	9	3	8	14	14	10	10
29	108	+2	+4	+7	0	+5	+4	+7	+9	+5	+7
30	120	0	4	2	8	6	5	5	10	5	12
31	104	24	14	10	15	19	10	6	10	14	12
32	115	10	3	20	20	15	20	15	20	15	15
33	160	40	30	25	20	25	25	20	30	27	20
34	120	0	10	25	20	15	20	10	15	14	0
35	100	2	8	10	15	10	20	12	8	11	10
36	104	14	14	16	12	4	14	9	15	12	14
37	80	+5	+5	+10	+10	+4	+8	+10	+5	+7	+3
38	154	4	4	14	18	29	20	19	20	16	35
39	95	13	10	7	20	15	11	20	21	15	15
40	105	20	5	5	5	5	5	10	12	9	15
41	110	20	35	25	20	30	20	22	20	24	25
42	95	0	10	10	10	15	10	15	15	11	22
43	115	5	10	10	10	15	10	15	10	11	10
44	94	4	5	2	8	12	7	6	12	7	7
45	115	5	3	5	5	8	5	7	0	5	5
46	90	0	0	+5	20	15	15	10	5	8	5
47	110	10	15	20	10	12	10	10	10	12	10
48	110	15	15	10	15	15	17	18	20	14	20
49	90	6	12	16	18	18	20	15	20	16	20
50	100	+5	0	0	+5	+4	+10	+10	+10	+6	+15

+ indicates rise instead of fall in blood pressure.

finds that 11 cases showed an average rise during the first week ranging from two to nine mm. of mercury and 10 cases showed an average rise from one to 15 mm. of mercury during the second week. Thirty-nine cases responded with some fall in diastolic pressure during the first week and 40 cases during the second week, as follows: discounting all falls below 10 mm. of mercury, 20 cases responded with an average fall from 11 to 20 mm. and five cases with an average fall from 21 to 31 mm. of mercury during the first week.

During the second week, 16 cases responded with an average fall of 11 to 20 mm. of mercury and five cases responded with a fall ranging between 21 and 43 mm. of mercury.

Table 4 illustrates the number of cases of the series with their respective

TABLE IV
Summary of Effects of Magnesium Sulphate on Diastolic Pressure

No. of Cases Showing	3 Hours After Injection	1 Day After	2 Days After	3 Days After	4 Days After	5 Days After	6 Days After	7 Days After	2nd Week After
No drop 0-5	17	17	16	9	5	7	6	6	6
Drop 6-10	7	8	9	11	9	11	13	10	12
Drop 11-15	7	9	5	9	13	7	10	11	9
Drop 16-20	4	5	4	11	5	11	8	9	7
Drop 21-25	3	1	4	0	2	2	2	1	3
Drop 26-30	2	2	2	1	3	1	1	3	1
Drop 31-35	0	1	1	0	0	1	1	0	1
Drop 36-40	1	0	0	0	1	0	0	0	0
Drop 41-45	0	0	0	0	0	0	0	1	1
Rise	9	7	9	9	12	10	9	9	10

falls in diastolic pressure on successive days of the study. The last column denotes the average fall during the second week of study. It is quite apparent from this table that the number of cases showing a constant fall in the diastolic pressure throughout the period of observation is fairly consistent.

II. EFFECT OF MAGNESIUM SULPHATE ON THE SYMPTOMS OF HYPERTENSION

The patients who came under our care did not come seeking relief from their hypertension; they came because they were suffering from a number of annoying and persisting symptoms. Our own observations, which coincide with those of other authors, disclose the fact that the following symptoms

are most commonly encountered in hypertension: (1) headache, (2) insomnia, (3) vertigo, (4) hot flashes, (5) head noises, and (6) nervousness.

Headache was the most prominent symptom occurring in 36 cases. Eighteen of these cases experienced complete relief for a period of two weeks after a single injection of .035 gm. of magnesium sulphate per kilo of body weight. Ten cases experienced moderate relief for a similar period. Six experienced relief for a period longer than four weeks. Two cases were not relieved at all.

Insomnia was the next most frequent symptom complained of. This symptom was found in 30 of our cases. Eighteen of these cases experienced relief for a period of two weeks after the first injection. In the greater number of these cases that were greatly disturbed by restlessness with only two or three hours of sleep per night, it was found that after injection they were able to have a good night's rest of seven to nine hours sleep. Three cases experienced relief for more than two weeks. Seven cases experienced moderate relief and two cases had no relief.

Vertigo. Twenty-seven cases of the series complained of vertigo. Nineteen were relieved for two weeks after the first injection. Three cases were relieved for a period longer than two weeks. Five cases had moderate relief.

Hot Flashes. Twenty cases complained of hot flashes. Ten were relieved for a period of two weeks after the first injection. Five cases were relieved for a longer period. Four cases were relieved only moderately. One case was not relieved.

Head Noises. Ten cases of our series complained of head noises which include buzzing in the ears. Six were relieved for a period of two weeks after the first injection. Two cases were relieved for a period longer than two weeks. Two cases were relieved for one week only.

Nervousness. Fifteen cases complained of nervousness. Nine were relieved for a period of two weeks after the first injection. Four cases were relieved for a longer period than two weeks. Two were only moderately relieved.

It is interesting to note that most patients complained of a multiplicity of symptoms. When the injection of magnesium sulphate produced relief, there was an amelioration of all the symptoms experienced by the patient. The effect of magnesium sulphate upon the blood pressure did not run parallel in a great number of cases with the relief of symptoms because where there was no marked, or only a moderate effect on the blood pressure, there was a considerable amelioration of symptoms.

CONCLUSIONS

1. The parenteral administration of magnesium sulphate had a distinct effect in reducing the systolic pressure in 40 cases of a series of 50 consecutive cases of hypertension. The effect was sustained for a period of at least two weeks.

2. The parenteral administration of magnesium sulphate had a definite effect in reducing the diastolic pressure in 25 cases of the same series and the effect was sustained for a period of two weeks in 21 cases.

3. The parenteral administration of magnesium sulphate had a distinct ameliorating effect on the symptoms of hypertension; viz., headache, vertigo, insomnia, hot flashes, head noises and nervousness.

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EXPERIMENTAL AND CLINICAL STUDIES OF ERGOTAMINE

V. THE ACTION OF ERGOTAMINE ON THE SYMPATHETIC NERVOUS SYSTEM STIMULATED BY EPINEPHRINE. STUDIES OF THE METABOLIC RATE, PULSE RATE, BLOOD PRESSURE, BLOOD SUGAR AND THE TOTAL LEUKOCYTE COUNT*

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IN A PREVIOUS PAPER¹ it was shown that in human subjects, under basal conditions, ergotamine had little or no effect on those motor divisions of the sympathetic nervous system concerned with the regulation of the blood sugar level or the basal metabolic rate. Evidence was given for the belief that the slowing of the pulse was the result of vagus stimulation rather than depression of the sympathetic. It was suggested at that time that the failure of ergotamine to depress certain of these motor functions of the sympathetic nervous system might be explained if the latter were inactive² in the basal state and therefore either insusceptible to the action of ergotamine or incapable of exhibiting its effect. Therefore, it was decided to study the action of ergotamine on the sympathetics which had been stimulated by epinephrine.

METHODS

The subjects were young healthy adults many of whom had served as subjects in previous experiments with ergotamine and were accustomed to the procedures employed. Observations were made of the combined effects of the drugs on the blood sugar level, metabolic rate, pulse rate, blood pressure and total leukocyte count. The following plan was followed. Six hours after a light breakfast the subject was placed in bed and allowed to rest quietly for at least an hour. Following the rest period there was a preliminary period during which the pulse rate and blood pressure were determined at frequent intervals until a basal level was reached. At the end of this time the basal metabolic rate was determined and a sample of blood drawn for determination of the blood sugar. In the studies of the leukocyte count, which were made separately, successive counts were made at the end of the rest period until a basal level was reached. After a short rest to allow the subject to recover from these procedures, epinephrine (0.5 or 1.0 mg. intramuscularly) and ergotamine (0.5 mg. subcutaneously) were injected and the metabolic rate, pulse rate, blood pressure, blood sugar

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concentration and total leukocyte count were determined at suitable intervals. In some of the subjects separate studies were made to compare the effect of ergotamine when given before the epinephrine with its effect when given after. In the others the ergotamine was given either before or after the epinephrine. When ergotamine was given first the time interval between the injection of ergotamine and epinephrine was approximately 10 to 15 minutes to allow the ergotamine to develop its effect. When the epinephrine was injected first the ergotamine was given immediately afterwards. In all cases control studies were made of the effect of epinephrine and of ergotamine alone.

The metabolic rate was determined by means of a spirometer and an analysis of the expired air (Haldane). The pulse was counted with a stop watch; when possible it was counted for a full minute. The blood pressure was determined with a mercury sphygmomanometer by the auscultatory method. Determinations of the blood sugar were made according to the method of Folin.³ All the leukocyte counts were made by a single observer, using special pipettes and counting chamber calibrated by the Bureau of Standards. The same pipettes and chamber were used throughout the experiments. Duplicate counts were made at each period and repeated unless they checked closely.

TABLE I

The Effect of Ergotamine (0.5 mg. Subcutaneously) on the Response of the Metabolic Rate to Injections of Epinephrine

Subject	Metabolic rate before injection per cent	Metabolic rate after injection* per cent			
		15 min.	30 min.	60 min.	120 min.
J. Y. (1.0 mg. epinephrine)					
Epinephrine control	-12	+30	+26	+18	+3
Ergotamine—Epinephrine	-17	+41	+11	-4	-18
Epinephrine—Ergotamine	-7	+6	+13	+9	±0
W. T. (1.0 mg. epinephrine)					
Epinephrine control	-7	+37	+32	+23	+1
Ergotamine—Epinephrine	+2	+27	+38	+25	+5
Epinephrine—Ergotamine	-3	+18	+18	+18	+4
H. F. (1.0 mg. epinephrine)					
Epinephrine control	-5	+20	+35	+21	+1
Ergotamine—Epinephrine	-6	+22	+32	+30	+1
Epinephrine—Ergotamine	+1	+8	+22	+28	+11
M. T. (0.5 mg. epinephrine)					
Epinephrine control	+16	+24	+22	+28	+17
Epinephrine—Ergotamine	+8	+22	+23	+29	+15
E. P. (0.5 mg. epinephrine)					
Epinephrine control	+7	+17	+25	+15	+4
Epinephrine—Ergotamine	±0	+18	+25	+15	-1
W. S. (0.5 mg. epinephrine)					
Epinephrine control	-5	-2	+6	+13	-6
Ergotamine—Epinephrine	-2	+16	+25	+13	-7

* The drugs were given in the order named in the various experiments. The time refers to the period after the injection of epinephrine. When the epinephrine was given first the ergotamine was injected immediately afterward. When the ergotamine was injected first a period of 10 to 15 minutes elapsed before the injection of epinephrine.

RESULTS

The results are summarized and shown graphically in the accompanying tables and charts. The effect on the metabolic rate was studied in six subjects, three of whom were given 1 mg. and three 0.5 mg. of epinephrine each. When the ergotamine was given *after* an injection of 1 mg. of epinephrine, the metabolic rate failed to increase as greatly as when the same amount of epinephrine was given alone. When ergotamine was injected *before* the epinephrine it failed to modify the effect of the latter, except that in one subject the metabolic rate fell to the initial level sooner than when epinephrine alone, or epinephrine followed by ergotamine, was given. Of the three subjects who were given 0.5 mg. of epinephrine two were given ergotamine after the epinephrine and one before. In the former ergotamine had no influence on the increase in metabolic rate caused by the epinephrine, while in the latter the rate was higher after the injection of both drugs than after epinephrine alone (table 1, figure 1).

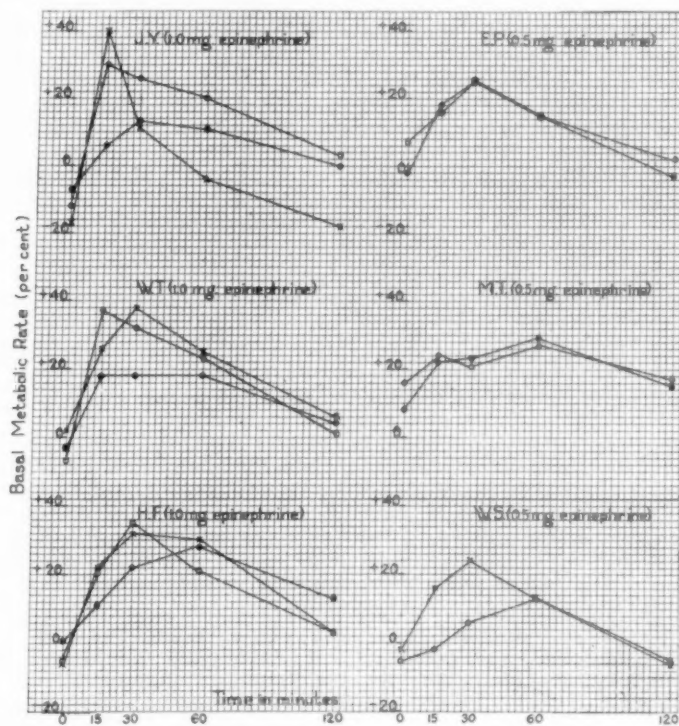


FIG. 1. The effect of ergotamine (0.5 mg. subcutaneously) on the response of the basal metabolic rate to an injection of epinephrine. The open circles represent experiments in which epinephrine alone was given; the crosses, those in which the ergotamine was given before the epinephrine; and the solid dots, those in which epinephrine was injected before the ergotamine. The initial values are those obtained before the injections. The time refers to the intervals after the injection of epinephrine. When epinephrine was injected first, the ergotamine was given immediately afterwards. When ergotamine was injected first, a period of 10 to 15 minutes elapsed before the injection of epinephrine.

In six subjects the effect of ergotamine on the hyperglycemic response to the injection of epinephrine was irregular but resembled somewhat its effect on the metabolic rate (table 2). Because of the variation in the basal

TABLE II
The Effect of Ergotamine (0.5 mg. Subcutaneously) on the Hyperglycemia Caused by an Injection of Epinephrine

Subject	Blood sugar before injections mg. per 100 c.c.	Blood sugar (mg. per 100 c.c.) after injection*			
		15 min.	30 min.	60 min.	120 min.
J. Y. (1.0 mg. epinephrine)					
Epinephrine control	73	95	105	105	114
Ergotamine—Epinephrine	92	91	102	133	115
Epinephrine—Ergotamine	95	100	107	87	
W. T. (1.0 mg. epinephrine)					
Epinephrine control	73	93	114	121	108
Ergotamine—Epinephrine	92	91	101	133	114
H. F. (1.0 mg. epinephrine)					
Epinephrine control	67	190	133	153	118
Epinephrine—Ergotamine	67	89	94	138	149
M. T. (0.5 mg. epinephrine)					
Epinephrine control	71	77	82	115	93
Epinephrine—Ergotamine	68	68	81	115	108
E. P. (0.5 mg. epinephrine)					
Epinephrine control	75	69	93	76	74
Epinephrine—Ergotamine	71	89	105	105	82
W. S. (0.5 mg. epinephrine)					
Epinephrine control	77	80	89	118	105
Ergotamine—Epinephrine	73	105	105	95	91

* The drugs were given in the order named in the various experiments. The time refers to the interval after the injection of epinephrine. When the epinephrine was given first the ergotamine was injected immediately afterward. When the ergotamine was injected first a period of 10 to 15 minutes elapsed before the injection of epinephrine.

level of the blood sugar in the different experiments the effect of ergotamine is best determined by comparing the increase over the initial level in each experiment (figure 2). Thus compared, the hyperglycemic effect of 1 mg. of epinephrine was somewhat less when ergotamine and epinephrine were given than when the same amount of epinephrine was given alone. In the subject (J. B. Y.), in whom the effect of ergotamine given before and after the epinephrine was compared, the inhibiting effect of ergotamine was greater when it was given after the epinephrine. When ergotamine was injected before the epinephrine there was an early inhibition of the hyperglycemia, followed by an increase in the blood sugar at the one hour period to as high a level as occurred after epinephrine alone, but a more rapid return toward the initial level. In subject H. F. the injection of ergotamine after epinephrine resulted in a smaller increase than with epinephrine alone, except that at the end of two hours the blood sugar was higher than at the end of an hour and was above the level reached in the control study

at the same period. Little effect of the ergotamine was noted in the three subjects who were given 0.5 mg. of epinephrine. In one (E. P.) the rise in blood sugar was slightly greater after both ergotamine and epinephrine than after epinephrine alone.

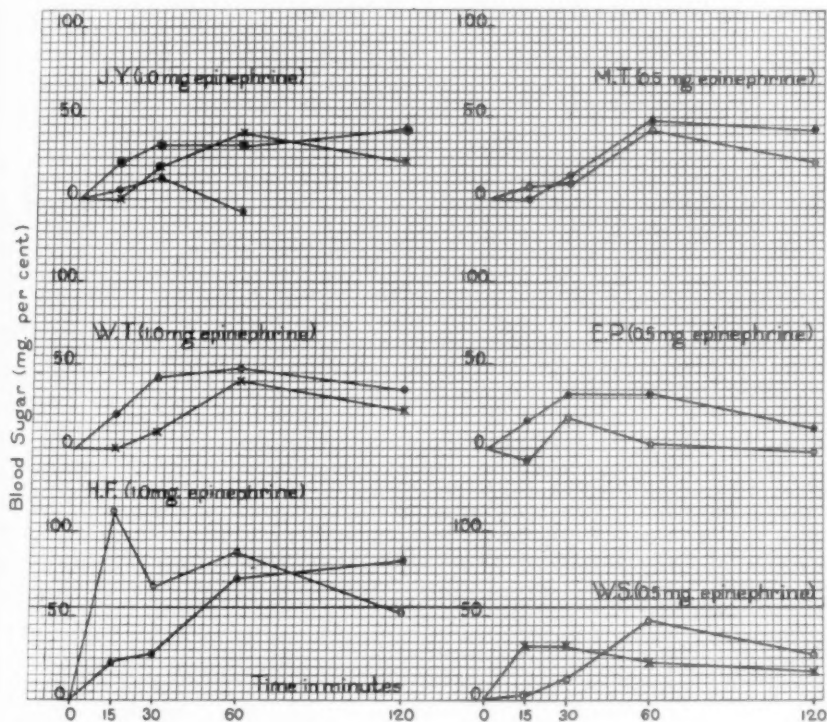


FIG. 2. The effect of ergotamine (0.5 mg. subcutaneously) on the hyperglycemia caused by an injection of epinephrine. In this figure the differences between the initial values and those found after injection are plotted rather than the actual values, the initial value in each case being taken as zero. The open circles represent experiments in which epinephrine alone was given; the crosses those in which ergotamine was given before the epinephrine; the solid dots, those in which epinephrine was injected before the ergotamine. The time refers to the intervals after the injection of epinephrine. When epinephrine was injected first, the ergotamine was given immediately afterwards. When ergotamine was given first a period of 10 to 15 minutes elapsed before the injection of epinephrine.

There is a difference in the time after injection at which the effect of ergotamine and epinephrine on the pulse rate occurs. This makes it difficult to determine the influence of ergotamine on the action of epinephrine. In four of the six subjects the maximum pulse rate after the injection of epinephrine was somewhat less when ergotamine was given irrespective of whether the latter was given before or after the epinephrine (table 3). Furthermore, there was in general a tendency for the pulse rate to return to the basal level sooner and for the maximum pulse rate to be reached earlier after the injection of epinephrine when ergotamine was given. The latter finding is of no significance, however, being due simply to the failure

of the pulse rate to rise as high when ergotamine was given, the maximum consequently being reached earlier. In one subject the increase in pulse rate was greater when ergotamine was given before the epinephrine than

TABLE III

The Effect of Ergotamine on the Response of the Pulse Rate to an Injection of Epinephrine

Subject	Epinephrine Control			Ergotamine— Epinephrine*			Epinephrine— Ergotamine*		
	Basal pulse rate	Maximum pulse rate after injection	Time after injection	Basal pulse rate	Maximum pulse rate after injection of epinephrine	Time after injection of epinephrine	Basal pulse rate	Maximum pulse rate after injection of epinephrine	Time after injection of epinephrine
	Beats per min.	Beats per min.	Min.	Beats per min.	Beats per min.	Min.	Beats per min.	Beats per min.	Min.
J. Y. (1 mg. epinephrine)	66	102	26	65	96	5	71	96	13
W. T. (1 mg. epinephrine)	73	100	24	71	90	14	76	96	16
H. F. (1 mg. epinephrine)	71	116	37	75	108	30	75	102	34
M. T. (0.5 mg. epinephrine)	68	88	11				65	80	12
W. S. (0.5 mg. epinephrine)	69	84	55	60	88	8			
E. P. (0.5 mg. epinephrine)	64	80	4				62	80	4

* The drugs were given in the order named. When the epinephrine was given first the ergotamine was injected immediately afterward. When the ergotamine was given first an interval of 10 to 15 minutes elapsed before the injection of epinephrine.

when epinephrine was given alone, and in one the increase in the pulse rate was the same when epinephrine alone and epinephrine and ergotamine were given. Both of these subjects were given 0.5 mg. of epinephrine. In the experiments in which the ergotamine was given before the epinephrine a slowing of the pulse often occurred before the epinephrine was injected.

In six subjects the rise in diastolic blood pressure was greater when ergotamine and epinephrine were given than when epinephrine was given alone. The same was true of the systolic pressure except in one subject in whom the rise was the same in both experiments (table 4). The diastolic pressure showed relatively the greater increase. In general the rise was progressive following the injections, but in several instances there was a temporary drop in diastolic pressure below the initial level, usually occurring before the increase. This fall in pressure was not caused solely by the ergotamine, either directly or by modifying the action of epinephrine⁴ since it occurred nearly as often when epinephrine alone was given.

TABLE IV

The Effect of Ergotamine (0.5 mg. Subcutaneously) on Response of the Blood Pressure to an Injection of Epinephrine

Subject	Maximum Blood Pressure (mm. Hg)											
	Epinephrine control				Ergotamine— Epinephrine*				Epinephrine— Ergotamine*			
	Basal		After epinephrine injection		Basal		After epinephrine injection		Basal		After epinephrine injection	
	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic
J. Y. (1 mg. epinephrine)	98	68	122	70	88	62	122	75	98	65	144	85
W. T. (1 mg. epinephrine)	104	64	140	66	100	66	152	74	102	60	144	78
H. F. (1 mg. epinephrine)	118	72	156	76	120	70	156	82	120	70	156	76
M. T. (0.5 mg. epinephrine)	100	60	108	66					96	58	130	78
W. S. (0.5 mg. epinephrine)	114	70	124	74	106	70	134	80				
E. P. (0.5 mg. epinephrine)	106	64	122	66					100	62	130	66

* The drugs were given in the order named. When the epinephrine was given first the ergotamine was injected immediately afterward. When the ergotamine was given first a period of 10 to 15 minutes elapsed before the injection of epinephrine.

In four subjects ergotamine alone had little effect on the total leukocyte count but in one the count was lowered slightly, and in another there was an increase which was not as great, however, as occurred with epinephrine. There was a slight tendency for ergotamine to inhibit the increase in leukocytes which followed the injection of 0.5 mg. of epinephrine (table 5), but this effect is less marked when the results are compared on the basis of the increase over the initial level (figure 3). When comparison is made in the latter manner there is no constant relation between the effect of ergotamine and the time of its injection. In each of the four subjects ergotamine caused a partial inhibition of the rise in leukocytes following the injection of epinephrine in one or the other of the two experiments in which both drugs were given, but in some it occurred when the ergotamine preceded and in others when ergotamine followed the epinephrine. In some of the experiments the injection of both drugs caused a greater rise than occurred with epinephrine alone.

TABLE V

The Effect of Ergotamine (0.5 mg. Subcutaneously) on the Leukocytosis Caused by the Injection of Epinephrine

Subject	Total leukocyte count before injections	Total leukocyte count after injections*					
		15 min.	30 min.	45 min.	60 min.	120 min.	
H. F.	Epinephrine control	7,350	8,800	10,320	11,300	10,580	6,760
	Ergotamine control	7,260	8,180	8,320	7,580	8,040	8,140
	Ergotamine—Epinephrine	8,360	11,040	10,360	9,880	9,400	7,240
	Epinephrine—Ergotamine	6,140	8,960	9,160	8,680	8,240	6,600
A. C.	Epinephrine control	6,710	7,280	9,220	9,380	8,480	6,920
	Ergotamine control	5,280	4,100	4,260	4,580	5,260	5,420
	Ergotamine—Epinephrine	5,675	7,075	7,650	8,975	7,720	7,500
	Epinephrine—Ergotamine	5,425	7,475	6,300	5,825	5,750	5,750
G. O.	Epinephrine control	7,650	11,800	10,780	10,420	9,160	8,720
	Ergotamine control	8,500	9,080	8,420	8,740	8,160	8,350
	Ergotamine—Epinephrine	7,425	15,150	12,425	9,650	9,000	7,450
	Epinephrine—Ergotamine	7,860	11,225	8,625	8,750	8,675	6,450
F. T.	Epinephrine control	5,680	7,440	7,760	7,600	6,120	6,080
	Ergotamine control	4,830	4,600	6,275	6,525	6,225	5,820
	Ergotamine—Epinephrine	7,440	7,595	8,275	7,350	7,225	5,700
	Epinephrine—Ergotamine	5,640	7,100	8,375	7,875	7,350	5,675

* The drugs were given in the order named in the various experiments. When both drugs were given the time refers to the interval after the injection of epinephrine. When the epinephrine was injected first the injection of ergotamine followed immediately. When ergotamine was given first an interval of 10 to 15 minutes elapsed before the injection of epinephrine.

DISCUSSION

It is evident that under the conditions of these experiments ergotamine may inhibit slightly the stimulating action of epinephrine on some functions of the sympathetic, but the inhibition is irregular and far from complete. Few similar studies have been reported and they deal only with the pulse rate and the blood sugar. Goldman⁵ was unable to abolish or reverse the effect of epinephrine on the pulse rate with ergotamine. According to Moretti⁶ the increase in blood sugar caused by epinephrine is diminished (or prevented?) by ergotamine. A similar effect is reported by Coelho and de Oliveira.⁷ Others have reported contradictory results in conditions such as thyrotoxicosis in which a stimulation of the sympathetic may be present. These reports have been summarized by us in an earlier paper.¹ In our experiments on dogs⁸ ergotamine was found to have less effect on the epinephrine hyperglycemia than was observed in the present study.

The effect of the two drugs on the blood pressure is most probably one of summation of individual reactions. We have shown that under basal conditions ergotamine increases the blood pressure,¹ the diastolic pressure principally. It is probable that this is the result of a direct action on the

vessels.⁴ Epinephrine causes mainly an increase in systolic pressure. The observed effect of the two drugs is therefore similar to what would be expected from the effect of each alone. In animals, and with relatively much larger doses, ergotamine may neutralize or reverse the effect of epinephrine on the blood pressure. No such effect was observed in these experiments.

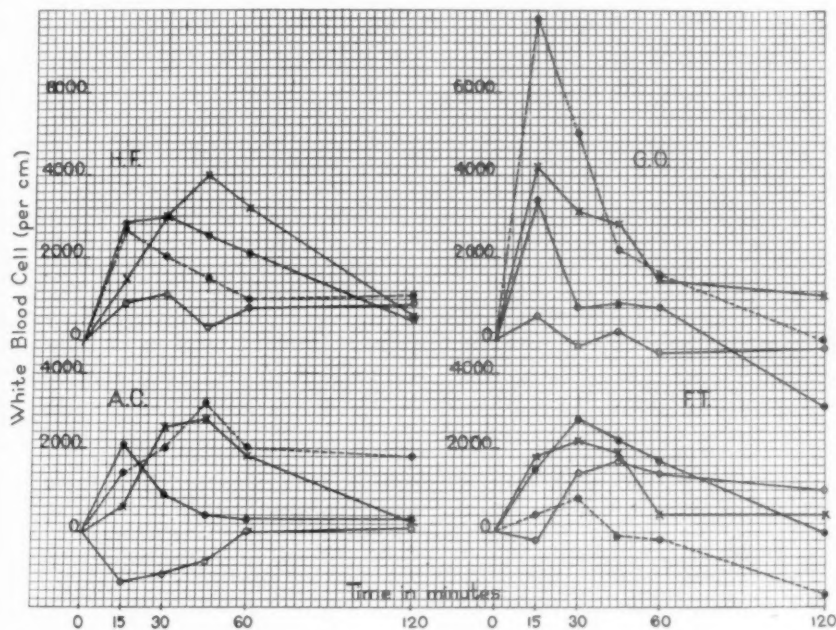


FIG. 3. The effect of ergotamine (0.5 mg. subcutaneously) on the leukocytosis caused by an injection of epinephrine. In this figure the differences between the initial values and those found after injection are plotted rather than the actual counts, the initial count in each case being taken as zero. The crosses represent experiments in which epinephrine alone, the circles experiments in which ergotamine alone, was given. The solid dots with a solid line represent experiments in which epinephrine was given before the ergotamine; the solid dots and broken lines those in which ergotamine was injected before the epinephrine. The time refers to the intervals after the injection. When both drugs were given it refers to the intervals after the injection of epinephrine. When epinephrine was injected first the ergotamine was given immediately afterwards. When ergotamine was given first, a period of 10 to 15 minutes elapsed before the injection of epinephrine.

With respect to the pulse rate, the pulse slowing action of ergotamine is opposed to the tachycardia caused by epinephrine and the effect of the injection of the two drugs depends on the balance between these two opposing actions. Most, if not all, of the ergotamine effect is, we believe, the result of a stimulation of the vagus and not a depression of the sympathetic. The preponderance of the sympathetic stimulation by epinephrine agrees well with the preponderance of the sympathetics of the heart under normal conditions, and explains the failure of ergotamine to cause any significant inhibition of the tachycardia caused by epinephrine. Whether any of the slight effect of ergotamine is the result of a depression of the sympathetic is diffi-

cult to determine. However, for reasons discussed below it is possible that ergotamine may possess such an action to a slight extent.

The influence of ergotamine on the leukocytosis caused by epinephrine was so irregular that no constant inhibitory action can be attributed to it. It should be noted, however, that in all these experiments the dose of epinephrine was only 0.5 mg.

When the experiments in which 0.5 mg. of epinephrine was given are compared with those in which 1.0 mg. was used the results are the opposite of those which would be expected, the ergotamine inhibiting the actions of 0.5 mg. less than it inhibited the action of double this amount of epinephrine. This offers some support for the theory that ergotamine is able to inhibit the motor sympathetics only when the latter are stimulated and even then (with the doses used) only partially and at the higher levels of stimulation. It may be significant that the greatest effect of ergotamine was observed in the experiments on the metabolic rate and the blood sugar. Both are functions which, as we have shown, are not influenced significantly by ergotamine under basal conditions. Both functions are probably inactive under basal conditions but are susceptible to relatively great and rapid stimulation with epinephrine. Further support for this conception of the mode of action of ergotamine is found in the studies of Wilder.⁹ This author has shown that the actions of certain drugs on the autonomic nervous system exhibit quantitative and qualitative differences which are related to the level of activity of the functions studied (the pulse rate and blood pressure in particular). The greater the activity the less susceptible are these functions to stimulating influences and the more sensitive to depressants; the less the activity the more affected by stimulation and the more resistant to inhibition. This general reaction, according to the author, constitutes a biologic law to which he has applied the term "law of the initial value" ("Ausgangswertgesetz"). Such a "law" is in conformity with the results of this and our previous studies. It will explain the many conflicting reports of the action of ergotamine in clinical experiments. If, to the factor of "stimulation level" one adds the necessity of employing small doses of ergotamine, the partial and irregular inhibition found in man seems more understandable. It is possible also that variations in the rate of absorption of the epinephrine and ergotamine may contribute to the irregularities in experiments such as these.

SUMMARY

Ergotamine, in doses of 0.5 mg. given subcutaneously, inhibited partially the increase in metabolic rate and the hyperglycemia which an injection of 1 mg. of epinephrine caused in normal subjects. The effect was somewhat greater and more constant when the ergotamine was given after the injection of epinephrine. When 0.5 mg. of epinephrine was given, ergotamine had little or no effect. The injection of ergotamine and epinephrine caused a greater increase in blood pressure than resulted from an injection of epi-

nephrine alone. The maximum pulse rate was slightly less when both ergotamine and epinephrine were given than when only epinephrine was injected. Ergotamine had no constant effect on the increase in the total leukocyte count which occurs following an injection of 0.5 mg. of epinephrine. Evidence is given for the belief that in man ergotamine is able to depress significantly certain functions of the sympathetic only when the latter are stimulated and that this depressing effect is directly proportional to the degree of sympathetic stimulation.

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PSYCHIATRIC INVESTIGATION IN INTERNAL MEDICINE*

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THERE is nothing novel in the idea that adequate medical care cannot be given to a patient unless his mental and emotional difficulties are understood. However, it seems to us that at present little of a concrete nature is being done in many medical departments in this country to apply this idea. The usual routine consists of a thorough study of the patient for the purpose of ruling out any organic pathology, and this being satisfactorily accomplished, he is discharged with only some such diagnosis as neurasthenia, and possibly a prescription for a sedative. Medical responsibility has seemed too often to end with the establishment of a diagnosis of a functional nervous disorder. We feel that these patients should be studied in a practical manner by a psychiatrist and assisted in the solution of basic problems. We shall briefly outline a few of these case histories and trace the subsequent course of the patient under psychiatric investigation.

CASE I

Mrs. G. S., aged 27 years, was referred to the medical service of the Wisconsin General Hospital on October 26, 1932, with a note from her physician stating: "Diagnosis obscure. Roentgen-ray might throw light on condition." Her chief complaint was vomiting. She dated the onset six months before admission, and stated that the vomiting took place shortly after eating. Although it did not occur after every meal at the onset, in the last few months it had become more frequent until by the time of admission there was only an occasional meal which was not followed by emesis. She denied nausea or epigastric pain and stated that her appetite was very good. The emesis was not affected by the type of food ingested. She had lost 20 pounds in weight since the onset of her difficulty. Physical examination showed the patient to be well built but somewhat undernourished. There were no significant abnormalities present. The clinical impression was neurotic vomiting. Routine laboratory studies including a gastric analysis showed no significant deviations from normal. The gastrointestinal series showed no abnormalities of the stomach or duodenal bulb. A barium enema showed some narrowing and poor filling of the sigmoid and terminal ileum, interpreted as probably the result of adhesions (patient had had an appendectomy and partial oöphorectomy in 1927). Soft diet, tincture of belladonna minims 10 before meals, together with sedatives and reassurance that no organic pathology existed, all entirely failed to affect the persistent vomiting.

The patient was transferred to the Neuro-Psychiatric Department on November 7, 1932. A preliminary conversation failed to reveal anything except an unhappy marriage. The patient appeared very unstable. She was distinctly tense, could not sit quietly, was evidently embarrassed and unwilling to go into details on the subject of her marriage. To facilitate matters 6 c.c. (grs. 4) of sodium amytal were administered intravenously. The patient became mildly exhilarated, all hesitancy and

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embarrassment disappeared and she gave the following history rapidly and with evident relief. Her childhood had been uneventful; during her school days she had entertained the idea that she might become a nurse but abandoned it because she was "easily upset by things." Shortly after leaving high school, she fell in love with and married her present husband. All went well until the birth of the first child. At this time the husband came home drunk and vomited in her presence. This resulted in the first of a long series of quarrels. Intercourse, which up to this time had been pleasing to the patient, now became definitely distasteful and she was conscious of vague pelvic pain. Her physician recommended oöphorectomy and salpingectomy. At the time of the operation, the physician said to her: "Of course you realize the seriousness of this operation; it will not only affect you physically, but in other ways as well." The postoperative course was physically uneventful, but the tactless warning of the doctor upset the patient emotionally. She entertained fears that she would be crippled sexually, or that she would be "different from other women." Returning home, she began pleading various excuses to escape intercourse, "backache—the operation," etc. On one occasion she was forced to use physical resistance.

Six months after the operation she went with her children on a visit to her grandfather, who was in poor health. This was made the excuse; in reality she was fleeing from her husband's attentions. Her last advice to him was, "Go out with other women; if you get a venereal disease that's the price you pay." After a short time the husband suddenly appeared and demanded that the patient return home with him. At this time the vomiting began. At first it occurred just after the evening meal. "He took no notice at first, then he got mad." All attempts at coitus precipitated further emesis. Gradually the periods of vomiting increased and the patient was unable to retain any meal.

Following this conference, the patient appeared less nervous, but the vomiting continued. Psychotherapy was instituted with suggestions as to a connection between the emesis and the sexual conflict, but it was left to the patient to draw the final conclusions. This she did six days later. At this time the vomiting suddenly ceased. The patient was kept in the hospital for four weeks longer without any recurrence of symptoms. Her future was then frankly discussed. Because of the children she was unwilling to contemplate divorce. Having conquered the emesis, she now felt that with a better understanding of her problem she could find readjustment in her marital life. Before her discharge, the situation with obvious reservations was discussed with the husband. A letter received February 15, 1933, from the patient stated that she had gained 15 pounds and was not vomiting at all.

Impression: Situational neurosis with accompanying coitophobia.

CASE II

Mrs. I. L., a housewife 28 years of age, was first seen by one of us in the medical out-patient department on April 21, 1932. Her chief complaint was "nervousness." She had had an almost continuous series of nasal colds with persistent cough during the past winter. She felt unduly fatigued. Her weight was exactly the same as two years before. At this interview the greatest emphasis was concentrated on the social history. The patient had had four children in a little over four years, the eldest being nine years old and the youngest four and a half years. Her husband had lost his job and she worked six and a half hours daily as an elevator operator. In addition she had household work and other domestic responsibilities to assume. One or more of the children had been ill almost all winter. On questioning she admitted that the husband drank intermittently, came home drunk and was very abusive. However, she gave the impression of great loyalty to him and did not volunteer complaints. She stated that she was not prone to worry about herself and would not have come into

the clinic now unless urged to do so by the visiting nurse, who wished her to be reexamined because of a previously diagnosed pulmonary tuberculosis.

The past medical history is of special interest in this case and will be given in some detail. She was first admitted to the hospital on September 24, 1928 and at that time also her chief complaint was "nervousness," which she then stated was of three years' duration. Other symptoms included easy excitability, palpitation, precordial pain, dyspnea on exertion, considerable muscular weakness and occasional syncope. About four months before this hospital admission, following a weight loss of 30 pounds in a few months, she had attended a chest clinic where she had been diagnosed as having pulmonary tuberculosis and had been sent to a tuberculosis sanatorium. She had remained there up to the time of the hospital admission, having been referred from the sanatorium to the hospital to have her "goiter" treated. She had gained 15 pounds in the four months at the sanatorium and also had regained a good appetite. The social history in the hospital record of this admission stated only: "Married six years. Husband living. Housework; busy with four children." The family history was of interest in that both father and mother died of pulmonary tuberculosis during the patient's childhood and there had been intimate contact. The significant findings on physical examination at this time were restlessness, moderate bilateral enlargement of the thyroid, the gland being soft and smooth, rapid pulse, blood pressure 150/90, tremor, hyperreflexia, moist palms and soles, no eye signs of hyperthyroidism, and no quadriceps weakness. Her basal metabolic rate was $+32$ and $+35$. On bed rest, mild sedatives and Lugol's solution minims 5 three times a day for four days the B.M.R. dropped to $+10$ and $+11$. The clinical impression was hyperthyroidism (exophthalmic goiter), and subtotal thyroidectomy was performed on October 26, 1928. The postoperative course was uneventful and the B.M.R. on October 15, 1928 was $+10$ and $+4$. The pathological report of the excised gland was colloid goiter. Stereoscopic roentgen-ray of the chest on September 25, 1928 was read as follows: "Apices relatively clear. Hilum lymph nodes show moderate increase. Several calcified nodules on either side. Calcified plaque anteriorly behind sternal end of fourth rib. Domes of diaphragm round and regular." This was interpreted as showing no evidence at all of recent parenchymal pathology.

She was readmitted on January 23, 1930. At this time her complaints were practically identical with those on her first admission. The physical findings also coincided very closely. The B.M.R. ranged from $+17$ to -1 . She was diagnosed as neurocirculatory asthenia and discharged with a recommendation for sedative medication.

This past medical history now leads up to the findings at the time of the examination cited at the beginning of this case report. The physical findings were in all respects similar to those previously reported. The extreme nervousness was obvious, the patient moving and twisting her hands continuously. The pulse rate was 106. There was a distinct tremor of the hands and evidence of marked vasomotor instability of the skin. The blood pressure was 146/96. It was questioned at this time if the patient had had recent active pulmonary tuberculosis or Graves' disease. It was believed that a situational neurosis superimposed on an unstable autonomic nervous system was the primary condition. In view of this she was referred to a psychiatric consultant. The point of interest in this case is the inference that if a careful social history had been elicited the patient might have been saved from sanatorium treatment for suspected tuberculosis and from thyroidectomy.

The patient was first seen in the psychiatric out-patient department on June 15, 1932. She presented a picture of extreme instability, the cheeks were flushed, the voice tremulous and there was almost constant wringing of the hands. With considerable persuasion she was finally encouraged to discuss her problem. The husband, a shiftless Irishman, was addicted to alcohol. While admitting his lapses, the patient at the same time loyally defended him. Her only condemnation lay in the

effect on the children. He would come home drunk and wake them up, frightening them "into tantrums by his carryings on." Her attempts at interference had resulted in physical violence to herself. The patient appeared at her wits end to know what to do. The conflict resulting between affection for her husband and despair over his actions had now reached an acute stage. She could see no future and appeared overwhelmed by the futility of her life. Practical suggestions such as six months' hospitalization of the husband for alcoholism, legal aid, etc., fell on deaf ears because the patient's affection and fear of her husband would not permit her to consider such measures. She was assured that only when the domestic difficulties were solved would there be an improvement in her own condition.

She was next seen in December 1932. At this time her condition appeared only slightly improved. Though still refusing to take any definite steps in the matter of her husband, she had become convinced of the connection between the home situation and her own nervousness. On March 1, 1933, the patient was again seen in the outpatient department. At this time a definite improvement was noted. She was more composed, sat quietly and was able to discuss her problem without the tremulousness previously noted. The husband had not been drinking for a period of two weeks. Symptoms of increased tension were elicited only when she conversed about the past. The patient left with the assurance that at any time, if the situation became too difficult, she should feel free to summon help.

Impression: Situational neurosis.

CASE III

Miss D. C., 23 years of age, was referred to the Wisconsin General Hospital on October 17, 1932, with a diagnosis of "tuberculosis of the left lung with pleurisy, or cardiac trouble." Her chief complaint was pain in the left chest. She dated the onset to about four years before. The pain had been intermittent in character, at times accompanied by a cough which was occasionally productive. She also complained of fatigue, attacks of vertigo associated with scotomata, tinnitus, dyspnea on sudden exertion, palpitation, anorexia, recent syncope and a weight loss of 16 pounds in the past three years.

Examination showed a moderately well developed and well nourished young woman. She was quite uncoöperative, jerked and quivered frequently and refused certain parts of the examination. There were no physical findings interpreted as significant. The clinical impression was anxiety neurosis. Routine laboratory examinations showed no significant abnormalities. Sputum examinations were reported as negative for tubercle bacilli on four occasions. The basal metabolic rate was -1 . Stereoscopic roentgen-ray of the chest showed no evidence of recent parenchymal pathology in the lungs. The sinuses were clear. Physiotherapy in the form of radiant heat and light to the left chest, high caloric diet and reassurance that no serious organic pathology was present resulted in no appreciable alleviation of the patient's symptoms.

On November 11, 1932 the patient was seen in psychiatric consultation. She appeared sullen, antagonistic and was unwilling to discuss her problem. To all inquiries, the invariable answers were "I don't care" or "I don't want to talk about it." Questions as to why she had come to the hospital elicited merely a curt recitation of vague pains in the cardiac region.

On being transferred to the Neuro-Psychiatric Department for observation, the patient immediately went to bed and for several days refused to get up or talk at all. On November 21, 1932, 6 c.c. of sodium amytal (grs. 4) were administered intravenously. Almost at once the patient became loquacious. She talked not only freely but with evident relief at being able to express herself. The history obtained at this time may be briefly summarized. Until 1928 she had been entirely well. At this time the other students in school began calling her "bastard" and making fun of her.

Many of her friends refused to go with her and when she asked for a reason was told, "If you don't know you ought to be ashamed." Two years of this type of persecution resulted in an attitude of suspicion and depression. In 1930 she was driven to the point of questioning her mother and was told it was true that she was illegitimate. Confirmation of her fears caused the patient to shun society. She became conscious of real or imaginary comments of the neighbors. The attitude of antagonism developed rapidly as the patient became more self centered and introspective. On eliciting the above, suggestive psychotherapy was instituted. The situation was outlined to the patient and rationalized with her. On November 26, 1932 a second intravenous injection of sodium amytal (grs. 7) was given and the psychotherapeutic suggestions continued.

Following this treatment improvement was observed. She became more talkative, coöperative, and distinctly approachable. Further conferences (without sodium amytal) seemed to stimulate outside interests and resulted in the making of a number of creditable articles by the patient in the occupational therapy department. At the time of discharge, December 22, 1932, the patient appeared to be satisfactorily adjusted. It is interesting to note that the chest symptoms which began in 1928 corresponded to the onset of the emotional disturbance.

Impression: Anxiety neurosis.

The above examples selected from a large group illustrate the importance of the social history and the need of psychiatric investigation in certain medical cases. We feel that unless the patient's problem is considered from a psychiatric as well as a physical viewpoint, the examination is of necessity incomplete and frequently the results are disappointing. The use of sodium amytal in psychiatric study has been discussed in previous reports. Its use in abnormal mental conditions was reported by Bleckwenn¹ in 1929. As a valuable aid in analysis it has been used by Lorenz² and his associates since 1930. The technic of administration is simple, and consists of dissolving 1 gram of the preparation in 20 c.c. of distilled water. The clear fluid is then injected under aseptic conditions into the vein at the rate of 1 c.c. a minute. After the patient has received 2 to 8 c.c., he enters a stage of "excitement" or "talkativeness." At this point the injection is stopped and the analysis begun. It is our impression that sodium amytal is of value because, (1) it permits a rapid and thorough examination with (2) the minimal amount of embarrassment to the patient, and (3) suggestive therapy under this drug is more easily given and more readily absorbed.

SUMMARY

Three cases originally admitted to the medical service are reviewed. In each instance a definite social problem was present. These problems when submitted to psychiatric investigation resulted in improvement of the patient's condition.

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EDITORIAL

FEDERAL MEDICAL CARE OF THE UNEMPLOYED

THE PROFESSIONAL medical care of the indigent in the home and in the hospital has heretofore been almost entirely a burden borne by the medical profession unaided. Private philanthropy and public tax money have provided for the construction and operation of hospitals in which the institutional type of medical service could be rendered. The same sources have provided salaries for the pharmacists, nurses, social service workers, technicians, and laboratory physicians working in these institutions. There are, however, comparatively few practicing physicians, if we exclude the physicians of the state and city insane hospitals and tuberculosis sanatoria, who receive salaries for the professional care of indigent patients. The enormous amount of free work done by practicing physicians in the home, in office practice, in the out-patient departments, and on the hospital wards has been the chief burden and at the same time the chief pride of the medical profession. If the value of this free work could be estimated in monetary terms, it would certainly be found to constitute a very large fraction of the total cost of medical service to the indigent.

This present status under which so high a proportion of the true cost of medical care of the indigent is contributed by the physicians in the form of free professional service, is not a satisfactory solution of the problem. It has proved impossible for the profession to furnish adequate medical care to all who are in need. It is true that in many hospitals and in some out-patient clinics, as well as in much of the work done in offices and homes, the free patient has received the highest type of medical care. It can scarcely be denied, however, that it has often proved impossible for the medical profession, especially in these days of depression, to meet adequately all the demands for free work. It is to their credit that they have covered the field as well as they have, and that few indeed of the needy have failed to receive some measure of free medical care.

If the present status may be considered unsatisfactory from the point of view of the inavailability of adequate medical care for a portion of our large indigent population, it must also be considered equally unsatisfactory from the point of view of the medical profession. In a time of shrinkage in their income-producing practice they have felt themselves obliged to carry the burden of an ever increasing number of free patients who were an expense to them not only in time and effort but in actual cash outlay for transportation and medical supplies. Both lay and professional opinion has increasingly favored the view that the cost of the professional care of the indigent should be borne by the community at large. However, since the assumption of this responsibility by any division of the Government would of necessity entail some form of "State Medicine" on a large scale a considerable section

of the medical profession, which for the most part has accepted the principle, has nevertheless been opposed to any of the plans suggested for putting this principle into effect.

This Gordian knot has been swiftly cut by the Federal Emergency Relief Administration. The conception of their plan may be traced to the statement in Rule No. 1, Section B, which was promulgated on June 23, 1933.

"Grants made to the States from Federal funds under the Federal Emergency Relief Act of 1933 may be used for the payment of medical attendance and medical supplies for those families that are receiving relief."

After a brief period of gestation in the summer, the full plan has been delivered to the waiting public towards the end of September in the pamphlet entitled "Rules and Regulations, No. 7, Governing Medical Care Provided in the Home to Recipients of Employment Relief." By the time this editorial is published, a form of State Medicine affecting a number of millions of our citizens will be in effect throughout our country.

Because of the historical importance of this alteration in the conditions of the practice of medicine, and because it will affect to some extent all physicians and all medical institutions, the complete pamphlet is reprinted in the pages of this journal.*

The Federal Emergency Relief Administration purposes, subject to definite conditions, paying the practicing physician a fee for his medical services to the indigent. Similarly it will pay for emergency dentistry, for nursing, and for medical supplies. It will not pay physicians or institutions for medical treatment of the indigent rendered in hospitals or out-patient departments. The Federal Emergency Relief Administration defines the broad lines of policy and procedure; the State and local relief administrations are to formulate the local programs. Representatives of the organized medical, dental, nursing, and pharmaceutical professions, appointed by these professions, are to act in an advisory capacity to the State and local relief administrations in the formulation and adoption of the local programs, and in settling disputed problems. The individual physician retains his freedom to participate or not in the local program for his community, but if he desires to participate he must signify his willingness "to accept the regulations and restrictions inherent in such a program."

These "regulations and restrictions" will be finally defined in the local programs, but it is specified under the heading of procedure that the following requirements must be met. The physician must obtain a written authorization from the local relief officer before treating the patient; he must certify to the relief officer when he considers nursing care is desirable; he must present to the relief officer a written request for such drugs as he deems the patient needs; he must certify that delivery in the home is safe in each instance in which he undertakes to deliver a woman in the home; he must obtain a renewal of authorization whenever an acute illness lasts longer than

* Reprinted by permission of the Federal Emergency Relief Administration.

two weeks or requires more than ten visits or when a chronic illness is protracted beyond two or three months; he must submit monthly bills with specified data, the visits arranged in chronological order, the proper authorizations appended, etc.; and finally he must accept a fixed fee schedule which "shall be established on the basis of an appreciable reduction from the prevailing minimum charges for similar services. . . ."

The rules and regulations promulgated by the Federal Emergency Relief Administration show evidence of careful preliminary study of the problem and of a wish to accomplish the desired purpose with the least disturbance possible of the normal relations between physicians and patients. Yet it is evident that they leave some important practical questions undecided and that the justice of some of the positions taken may well be questioned. Among the first in importance of the omissions is the lack of a clear cut statement as to whether the indigent patient is to be required to choose his own physician or whether, in the case where he has none, the relief officer will select one for him. The latter alternative would constitute a long step in the direction of a governmental medical service. It will seem to many also that exclusion of hospitals and their physicians and of out-patient departments and their physicians from the benefits of the act is arbitrary and unjust. The majority of these institutions are incurring deficits in their attempt to provide treatment for an increasing number of indigent patients. Their physicians are called upon to give without recompense even more of their time to the care of the indigent than in more prosperous years. It may well be, however, that the new order of things will lead to a larger number of the indigent receiving care in their homes or in doctors' offices, and that thus the clinics and hospitals will indirectly receive economic help by a lightening of their load. The level of medical care for the patients affected will be maintained in these circumstances only if the physician in outside practice clearly distinguishes between those cases which do and those which do not require the facilities of a clinic for their adequate care. It is apparent that time will be required to disclose the advantages and disadvantages of the plan, and that new rulings may alter many of its features.

Our Government in these stirring days is manifestly proceeding upon the assumption that a state of emergency exists which warrants the extension of governmental action into many fields not previously included in its scope. The physician now falls into the company of the merchant, the manufacturer and the laboring man as one whose occupation is to some extent altered in its conditions by Federal decree. It must be pointed out that in the physician's case the change is a relatively minor one and that he has been left so far with entire liberty of action.

The people of this country have shown plainly their disposition to accept in good spirit the radical actions of the Government and, whether individually doubtful of the results or not, to use every effort to give to the new measures every chance for success. The medical profession should do no less. It should accept these rulings establishing a form of State medicine as

temporary and emergency measures and give its best efforts to the task of accomplishing their purpose, "the provision of good medical service at low cost—to the mutual benefit of indigent patient, physician, nurse, dentist and tax-payer."

RULES AND REGULATIONS

No. 7

GOVERNING MEDICAL CARE PROVIDED IN THE HOME TO RECIPIENTS OF UNEMPLOYMENT RELIEF

INTRODUCTION

The conservation and maintenance of the public health is a primary function of our Government. In this emergency, the ingenuity of Federal, State, and local relief officials is being taxed to conserve available public funds and, at the same time, to give adequate relief to those in need. To assist State and local relief administrations in the achievement of these aims, with regard to medical care, two steps have been taken: First, to define the general scope of authorized medical care, where the expenditure of Federal Emergency Relief Funds is involved; and second, to establish general regulations governing the provision of such medical care to recipients of unemployment relief.

GENERAL SCOPE

(Extracted from rules nos. 1 and 3, previously established)

Promulgated on June 23, 1933, rule no. 1, section (b), stated:

Grants made to the States from Federal funds under the Federal Emergency Relief Act of 1933 may be used for the payment of medical attendance and medical supplies for those families that are receiving relief.

The permission granted under this section (b) was more sharply defined in the same rule, in section (d), which stated in part:

These funds may not be used for the payment of hospital bills . . . , or for providing general institutional care. These necessary services to the destitute should be made available through State or local funds.

In the section on "Direct Relief" of rule no. 3, promulgated on July 15, 1933, medical care in the home was listed as item 6 in the list of the types of relief that may be provided to relief cases, viz:

"6. Orders for medicine, medical supplies and/or medical attendance to be furnished in the home." Under the same rule, adequacy of such relief is made "an obligation on the State Emergency Relief Administration and on all the political subdivisions of the States administering relief. . . ."

The scope of medical care as above defined shall be construed to include: Bed-side nursing care, as an adjunct to medical care; and emergency dental service for those families that are receiving relief.

REGULATIONS GOVERNING MEDICAL CARE PROVIDED IN THE HOME TO RECIPIENTS OF UNEMPLOYMENT RELIEF

The following regulations, governing the provision in the home of medical care (includes "medicine, medical supplies and/or medical attendance") to persons eligible for unemployment relief, are hereby established.

1. *Policy.* A uniform policy with regard to the provision of medical, nursing, and dental care for indigent persons in their homes, shall be made the basis of an agreement between the relief administration and the organized medical, nursing, and dental professions, State and/or local. The essence of such a policy should be:

(a) An agreement by the relief administration to recognize within legal and economic limitations, the traditional family and family-physician relationship in the authorization of medical care for indigent persons in their homes; the traditional physician-nurse relationship in the authorization of bed-side nursing care; the traditional dentist-patient relationship in the authorization of emergency dental care; and

(b) An agreement by the physician, nurse (or nursing organization), and dentist to furnish the same type of service to an indigent person as would be rendered to a private patient, but that such authorized service shall be a minimum consistent with good professional judgment, and shall be charged for at an agreed rate which makes due allowance for the conservation of relief funds.

The common aim should be the provision of good medical service at a low cost—to the mutual benefit of indigent patient, physician, nurse, dentist, and taxpayer.

The policy adopted shall be to augment and render more adequate facilities already existing in the community for the provision of medical care by the medical, nursing, and dental professions to indigent persons. It shall imply continuance in the use of hospitals, clinics, and medical, dental, and nursing services already established in the community and paid for, in whole or in part, from local and/or State funds in accordance with local statutes or charter provisions. Federal Emergency Relief Funds shall not be used in lieu of local and/or State funds to pay for these established services.

The phrase "in their homes" shall be interpreted to include office service for ambulatory patients, with the understanding that such office service shall not supplant the services of clinics already provided in the community.

2. *Procedure.* A uniform procedure for authorization of medical, nursing, and dental care in the home shall be established by each State and/or local emergency relief administration. This procedure shall not be in conflict with the following requirements:

(a) *Written Order.* All authorizations for medical, nursing, and dental care shall be issued in writing by the local relief officer, on the regular relief order blank, prior to giving such care; except that telephone authorization shall immediately be followed by such a written order; and provided that authorizations for bed-side nursing care shall be based on a recommendation by the attending physician, in cases where a physician is in attendance, who shall certify to the need for nursing service as part of the medical care. Authorizations for medicine and medical supplies shall also be issued in writing and, in general, such authorizations shall not be issued except upon written request of the physician authorized to attend the person for whose use they are desired.

(b) *Acute Illness.* Authorizations for medical care for acute illness shall be limited to a definite period and a maximum expenditure or number of visits (i.e., not more than 2 weeks or 10 visits), according to the standard agreement made between relief officials and physicians under regulation 1. Medical care in excess of this period shall not be authorized until after a reinvestigation of the case in the home by the local emergency relief administration.

(c) *Chronic Illness.* Medical care for prolonged illnesses, such as chronic asthma, chronic heart disease, chronic rheumatism, diabetes, etc., shall be authorized on an individual basis, and, in general, visits shall be limited in frequency (i.e., not more than 1 visit per week for a period not exceeding 2 or 3 months) by agreement. Nursing care for such chronic illnesses shall, in general, be authorized in accordance with the need for such care as indicated by the attending physician. If necessary, more frequent visits, by the physician or nurse, for an acute attack occurring in the course

of a chronic illness, may be authorized. Care for chronic illness authorized under this section shall supplement and not supersede existing community services, such as visiting nursing service or institutional care.

(d) *Obstetrical Care.* Authorization for obstetrical service in the home shall include an agreed minimum number of prenatal visits (where possible), delivery in the home, and necessary postnatal care. Due caution shall be exercised that this authorization for delivery in the home does not involve undue risk to the patient for whom hospital care may be imperative. The physician authorized to attend the confinement in the home shall be responsible for certifying to the local relief administration that, in his professional judgment, delivery in the home will be safe.

(e) *Special Services.* Medical and nursing services not covered above shall be authorized on an individual basis, subject to the general provisions of the agreement made under regulation 1. Special dental service shall be subject to a similar procedure.

Medical care shall not ordinarily be authorized by relief administrations for conditions that do not cause acute suffering, interfere with earning capacity, endanger life, or threaten some permanent new handicap that is preventable when medical care is sought.

(f) *Accessory Services.* Emergency dental care and bedside nursing service, for indigent persons in their homes, may be authorized subject to the existing general policy of the State and/or local relief administration.

(1) *Dental care* shall, in general, be restricted to emergency extractions and repairs. Dentists and dental care shall be subject to the same general restrictions indicated for physicians under regulation 1.

(2) *Bedside nursing care*, where authorized, shall conform to a procedure comparable to the one outlined for physicians above, and shall be provided under an agreement made between relief administrations and nursing organizations, State and/or local, under the same principles suggested for physicians under regulation 1. Standards of accredited local nursing organizations shall be followed by nurses giving authorized bedside nursing care to indigent persons in their homes. Such authorized bedside nursing care shall not supersede or supplant existing local official services giving such care under the provisions of local law.

(g) *Fee Schedule.* The agreement between the State and/or local relief administration and the organized professional groups of physicians, nurses, and dentists, State and/or local, established under regulation 1, shall include a fee schedule covering the basic and special services outlined in sections (b) to (f), inclusive, of this regulation. In the interests of simplified accounting it is suggested: That a flat rate be established, on a per visit basis for the usual care given to acute and chronic illness (sections (b) and (c) above), for attendance at confinement (section (d) above), for emergency extractions (section (f) above), and for a bedside nursing visit (section (f) above); and that all special services (medical, nursing, or dental) be covered by an agreed reduction from the usual minimum fee schedule for such services with an agreed maximum fee. A recognized differential in fee shall be established between a home and an office visit. All fees shall be established on the basis of an appreciable reduction from the prevailing minimum charges for similar services in the State and local communities, with due recognition of the certainty, simplicity and promptness of payment that authorization from the local relief administration insures.

This schedule shall only apply where the expenditure of Federal Relief Funds is involved and shall not preclude the payment of additional amounts from local funds.

Where bedside nursing care is authorized, flat rate per visit shall be established by agreement at not to exceed the certified cost per visit established for accredited visiting nursing organizations in the State or local district.

(h) *Bills.* Physicians, nurses (or nursing organizations), and dentists who are providing authorized medical care to indigent persons in their homes shall submit

to the local relief official, monthly (within 10 days after the last day of the calendar month in which such medical care was provided), an itemized bill for each patient. Each bill shall be chronologically arranged and shall contain at least enough information to permit proper audit (i.e., name, age, and address of patient; general nature of illness or diagnosis; whether home or office treatment; dates of service; and status of case at end of month—cured, sent to hospital, dead, needs further care, etc.). Bills for medical care shall be accompanied by the original written order for such care, except for cases in which medical service under an authorization has not terminated during the calendar month covered by the bill, in which cases the bill shall show, in addition to the details required above, the date and serial number of the outstanding order. Retroactive authorizations shall not be issued or honored for payment.

Bills for special and accessory services, outlined under sections (e) and (f) above, shall give full details of such services, and bills for medicines and medical supplies, under (i) below, shall be subject to the same general requirements. Bills for drugs shall list the name and quantity of each. The formula and number of each prescription costing more than 25 cents shall be submitted with or made a part of the pharmacist's bill.

NOTE. The submission of bills and their audit and authorization for payment will be simplified if the State Emergency Relief Administration provides a suitable bill form.

(i) *Medicine and Medical Supplies.* Physicians providing authorized medical care to indigent persons shall use a formulary which excludes expensive drugs where less expensive drugs can be used with the same therapeutic effect. When expensive medication is considered essential by the authorized attending physician it may be authorized after consultation with the local medical advisory committee.

Prescriptions for necessary drugs and medicine shall be restricted to the National Formulary or the United States Pharmacopeia. To avoid excessive expenditures for remedies of unknown or doubtful value proprietary or patent medicines shall not be authorized.

State and/or local relief officials are urged to make trade agreements with pharmaceutical organizations and druggists for uniform or reduced rates for prescriptions.

Authorizations for medical supplies shall be restricted to the simplest emergency needs of the patient consistent with good medical care.

In general, authorizations for medicine and medical supplies shall not be issued except upon written request of the physician authorized to attend the person for whose use they are desired.

3. *Authority.* The State emergency relief administration, responsible for the distribution of Federal and State Emergency Relief Funds to local relief administrations, shall give approval to such statements of policy, proposed fee schedules, and detailed procedures, governing the provision of medical, nursing, and dental care in the home to recipients of unemployment relief, as may be established by State and/or local relief administrations, in accordance with the provisions of regulations 1 and 2, above, before such policies, schedules, and procedures shall take effect. It shall be the responsibility of the State emergency relief administration to formulate a program of medical, nursing, and dental care for indigent persons in their homes, which shall not be in conflict with the provisions of regulations 1 and 2, above, and to make sure, by giving or withholding approval, that analogous programs formulated by local relief administrations shall not be in conflict with such State program.

(a) *State and Local Professional Advisory Committees.* State and local relief administrations shall request the presidents of the State and local medical, nursing, dental, and pharmaceutical organizations, respectively, to designate an existing committee or appoint a special committee, to advise them in the formulation and adoption

of adequate programs for medical, nursing, and dental care in the home for indigent persons. The relief administrations shall be responsible for the final adoption of such programs. The medical, nursing, dental, and pharmaceutical advisory committees can assist these administrations in maintaining proper professional standards and in enlisting the coöperation of the constituent, professional membership in such programs. Local medical, nursing, and dental programs submitted to the State relief administration for approval should be submitted to the appropriate professional advisory committee for comment, before final approval is given. The appropriate professional advisory committees should be consulted by relief administrations with regard to disputed problems of medical, nursing, and dental policy and practice.

(b) *Licensed Practitioners of Medicine and Related Professions.* When a program of medical care in the home for indigent persons has been officially adopted, participation shall be open to all physicians licensed to practice medicine in the State, subject to local statutory limitations and the general policy outlined in regulation 1, above. Physicians authorized by relief officials to give medical care under this program shall have accepted, or shall be willing to accept, the regulations and restrictions inherent in such a program. In order to provide adequate medical care it may be desirable for local relief officials to maintain on a district basis a list or file of physicians in the community who have agreed in writing to comply with the officially adopted program. Such a list of physicians should also facilitate a more equitable distribution of orders for medical services.

A similar policy and procedure shall be followed in the preparation of approved lists of nurses, dentists, and pharmacists. Licensure and/or registration to practice their respective professions in the State shall be a prerequisite to approval of graduate nurses, dentists, and pharmacists for authorized participation in the officially approved State program for the provision of medical care for indigent persons in their homes.

(c) *State Program for Medical Care to Indigent Persons in Their Homes.* When the State emergency relief administration has adopted a uniform program for medical, nursing, and dental care for indigent persons in their homes, in accordance with these rules, a copy of such program, including the statement of policy, fee schedules, and detailed procedures, shall be filed immediately with the Federal Emergency Relief Administration.

REVIEWS

An Index of Treatment. By various writers; edited by ROBERT HUTCHINSON, M.D., F.R.C.P. Tenth Edition, Revised. xviii + 1027 pages; 18 × 26 cm. William Wood and Company, New York. 1931. Price, \$12.00.

This, the tenth edition of a work first published in 1907, is suited to the needs of the general practitioner rather than to those of the specialist of any type. It includes medicine, surgery, gynecology, obstetrics, and practically all other branches in its scope, and of necessity, the treatment of many diseases is outlined in one plan only, rather than allowing several alternatives.

The section on diabetes mellitus, by Edmund Speggs, is quite complete. Several methods of dietetic treatment are fully outlined, the choice of method depending on the physician and patient. Directions for making up menus according to a dietary prescription are much clearer and more easily followed than those in most textbooks. High carbohydrate diets are only suggested, and except in the section on diabetes in children, a maximum of 100 gm. daily is given. Less attention is paid to surgical complications than is desirable. The section on the treatment of coma is clear and complete.

A special section on the treatment of diabetes in childhood, by George Graham, is included. It contains several useful suggestions, and advocates high carbohydrate diets. Tables of food composition, by A. J. Leigh, are rather complete and made up in an unusual and very helpful way, which should facilitate very much the calculation of diets.

The English origin of this book is emphasized by the assignment of five times more space to the treatment of gout than is devoted to the medical treatment of duodenal ulcer. Only one plan of treatment for duodenal ulcer is suggested. The suggestion that operation should be carried out as soon as possible after a hemorrhage is unusual, especially when contrasted to the conservative treatment of hemorrhage usually followed in this country.

The section on pneumonia is disappointing. Only one method of oxygen administration is suggested, that of the nasal catheter. Oxygen tents and chambers are not discussed, nor is the quantity of oxygen given mentioned at all. Serum treatment is dismissed in a short paragraph without recommendation even in Type I pneumonias. The recommendation of intravenous mercurials in the presence of a positive blood culture is startling.

Much useful information about nursing procedures, physiotherapy, and other methods of treatment is given. The almost exclusive use of the English system of weights and measures is a disadvantage, as most schools in this country are attempting to adopt the metric system. Likewise the frequent mention of English proprietary drugs, without the names of the manufacturers, is confusing. Spa treatment is emphasized; the health resorts in the United States are not mentioned. The introduction, by the editor, discusses the importance of a well organized plan of treatment, and serves to correlate the main contents of the book.

It is inevitable in a work of this type, with so many individual contributors, that some unevenness of value should occur. The average is high, however, and throughout the book there is evidence of care in preparation and organization. Many articles supplement each other. Indexing is complete. As a compact and ready source of

therapeutic information for the physician in active practice this book has a distinct field of usefulness.

T. N. C.

An Index of Prognosis and End-Results of Treatment. By various writers; edited by A. RENDLE SHORT, B.S., B.Sc. (Lond.), F.R.C.S. (Eng.) Fourth Edition, Fully Revised. xi + 599 pages; 18 × 26 cm. William Wood and Company, New York. 1932. Price, \$13.50.

This volume is a companion to the *Index of Differential Diagnosis and Index of Treatment*, issued by the same publishers, and follows the same general plan of organization. It includes practically all branches of medicine and surgery. The purposes of the work, as stated in the preface to the first edition and repeated in that of the present edition are:

"1. To set forth the results, and particularly the end-results of treatment, in such a form as will enable the practitioner to obtain a fair, unbiased, reasoned opinion as to the prospects of securing for his patient permanent relief, and the risks of such treatment.

"2. To furnish data by means of which, apart from the question of treatment, one may arrive at an accurate forecast of what will probably happen to the individual patient."

The book exhibits a degree of uniformity unusual in a composite work of this type. In general, the same plan is carried out in discussion of different diseases. Prognosis as to recovery from acute disease is discussed in general, together with effects of treatment. The incidence of complications and sequelae is outlined fully. In the sections on chronic diseases, prognosis as to ultimate recovery, retention of function, and ultimate duration of life are discussed.

The surgical articles, many of which are contributed by the editor, A. Rendle Short, are very interesting. Types of operation, mortality from operative procedures, immediate and late result of operation, with complicating factors, are fully outlined. Tables which can be read at a glance are included in many of the articles. Statistics, as a rule, are recent and carefully analyzed, and a satisfactory bibliography is usually included. Very full discussion is given those diseases which admit of either "medical" or "surgical" treatment. In this class falls the article on peptic ulcer, contributed by the editor.

The sections devoted to medical diseases are, as a rule, less formally written and not so well documented as the surgical articles, with fewer statistical tables; but in spite of this they are none the less interesting and informative. Articles on cardiovascular disease, largely contributed by C. F. Coombs, C. B. Perry, and E. J. Poynton are quite complete. Most of the neurological sections are by J. Purves-Stewart.

An especially valuable chapter on anesthetics is contributed by D. W. Buxton. Anesthetic hazards, effect of anesthesia on disease, incidence of complications from different anesthetics, and the choice of anesthetics for types of patients and operations are fully discussed.

This book should be a valuable addition to any physician's library. The information throughout is clear, accessible and well digested, and presented in a very interesting manner.

T. N. C.

Pediatrics. By HENRY DWIGHT CHAPIN, M.A., M.D., Professor Emeritus of Pediatrics, New York Post-Graduate Medical School, Columbia University; and LAWRENCE T. ROYSTER, M.D., Professor of Pediatrics and Head of the Department of Pediatrics, University of Virginia. xvi + 775 pages; 16 × 23 cm. William Wood and Co., Baltimore, Maryland. 1933. Price, \$7.00.

This is the seventh revised and enlarged edition of the standard textbook which was first published in 1910 under the title of *Diseases of Infants and Children*. It is an eminently practical book whose value to the profession is attested by the appearance of repeated new editions.

The first section deals with growth and development and includes a splendid chapter on the appraisal of the child. This is followed by excellent chapters on the feeding of newly born children and infants. The advances of the past five years in the knowledge of digestion and metabolism of food elements are well presented. An entire chapter is devoted to the latest conceptions of the vitamins. New sections on ketosis and alkalis have been added under diseases of the digestive tract.

Intelligence tests are described, as well as various diagnostic and therapeutic procedures. The chapter on diseases of the brain includes a concise discussion of lead poisoning. Another interesting new article is the consideration of erythroblastic anemia which the author placed in the class of primary anemias.

Finally there is a chapter on the care of dependent infants and children which should prove especially interesting to the general practitioner.

The main divisions of the book are based on the systems of the human body, to which are added a section on infectious diseases and one on the commoner surgical diseases. It is pleasing to note that the section on diseases of nutrition is completely separated from that on diseases of the digestive tract.

This book is useful and this new edition will prove valuable alike to pediatricians, practitioners and students.

A. H. F.

Biochemistry of Medicine. By A. T. CAMERON, M.A., D.Sc., F.I.C., F.R.S.C., and C. R. GILMOUR, M.D., C.M., F.R.C.P.(C.). 506 pages; 22.5 × 15 cm. Wm. Wood and Co., Baltimore, Maryland. 1933.

As the title implies, this book is written for the student of medicine rather than for the student of pure biochemistry. The authors have undertaken successfully to present to those in the medical profession a text which will correlate and interpret biochemical data with reference to their medical significance. There has been no attempt to present pure theoretical biochemistry except where such information would lead to a better understanding of the subject discussed.

The normal metabolism of carbohydrates, fats, and proteins is discussed in sufficient detail to enable the reader to appreciate the complete analyses of abnormalities in these fields. The authors have gone further than a mere statement of diseases and causes for they have given within the text those tests that are essential for the identification of the disease or corroboration of their diagnosis. Clinical symptoms, theoretical interpretations and chemical tests are presented in such a fashion as has rarely been found in a single text. The rare diseases are discussed in as much detail as past and recent investigations permit. The discussion of the abnormalities of protein metabolism is particularly complete.

The chapter headed "Metabolism of Water. Passage of water and dissolved substances across animal membranes. Edema and kidney function" is one of the most able of its kind. A vast subject is covered in a remarkably condensed and com-

plete fashion. The authors have covered the literature up to and including the latest publications. For example the short paragraph on the formation of the cerebrospinal fluid summarizes completely this important physiological process from the chemical viewpoint while the references cover the subject in theoretical and technical details.

Other than this there is a necessarily short discussion on respiration, a chapter on the endocrine secretions and a more or less outlined account on the vitamins, their sources and the functional disturbances caused by their deficiencies. To these have been added short chapters on gastric functional tests and liver tests, giving a short description of those used in most laboratories or those suggested in recent papers.

The authors have added to the value of the book by placing at the end of each chapter a short summary and the latest references which are pertinent to the subject discussed.

Biochemistry of Medicine is an excellent supplementary text for any professional man who wishes to review his biochemistry in terms of the cases he has seen or for the student who wishes to correlate his pure biochemistry with clinical data.

E. M. R.

Der dialektische Materialismus und die klinische Medizin. By Professor J. LIFSCHITZ. (Allukrainische Gesellschaft zur Förderung der kulturellen Verbindungen mit dem Auslande.) Paper. 80 pages. Medwydaw. Kharkiw. 1932.

This small monograph is essentially propaganda, setting forth the ideas and theories of Soviet Republicanism so far as the philosophic view of medicine is concerned. It is of little value, except to show the trend of scientific and philosophic thought as applied to medicine in present day Russia.

A. C. G.

Diet in Sinus Infections and Colds. By EGON V. ULLMANN. 166 pages. The Macmillan Company, New York.

In the introduction to his book the author states that "this work constitutes the first systematic attempt to apply the modern knowledge of nutrition to individuals who suffer from repeated colds and sinus infections." The attempt has not been wholly successful. The editor, it is true, rather than the author (whose training seems to have been chiefly in Vienna), must be responsible for the retention of foreign expressions, and the German phraseology transferred bodily into English. For example, phosphorus is "phosphor," lecithin is "lezithin," and chlorine is "chlor"; the adjectives "animalic" and "vegetabilic" occur throughout, and food is continually being "exploited." One chapter is devoted to a condensed and somewhat inaccurate exposition of elemental chemistry, and another to the estimation of urinary acidity, and urinary chlorides. The author deprecates the ingestion of too much water in the diet. He prefers alkaline foods, and believes in the reduction of the use of "animalic" proteins, as well as of carbohydrates whenever possible. Fruits and preserves should be used only when canned in glass jars. Curtasal should be used instead of salt.

One of the author's most emphasized aversions is to sodium chloride, to the excessive ingestion of which in the food he ascribes many ills. He states that it may be the cause of hyperacidity, and hence of bad breath which "is quite often due to the accumulation of acid in the stomach." He states that the intake of sodium chloride in excess of 8 gm. per day is "injurious to the full utilization of proteins," and that "its use leads to a craving—like nicotine, alcohol and opiates." "No one was ever harmed by taking too little or no salt." "The modern treatment which deprives

patients with high blood pressure and kidney disease of table salt is the best proof that man can get along without it." Finally appears the remarkable statement that "if sodium is 'eliminated in the intake,' the biological effect of calcium will be enforced, and the diet will work antiphlogistically."

The book contains statements such as the following: "Plums and prunes have a solvent effect on the catarrhs of the digestive tract." "Blackberries produce perspiration and dissolve mucus." "Sprue can be cured only with a diet of fresh strawberries." "Lemon juice has a caustic effect on the mucous membranes of the stomach, and is decalcifying to the enamel of the teeth, and may even lead to poisoning." "Onions should not be given in kidney diseases." Perhaps the most interesting fact about this book is that it is sponsored by a firm whose reputation in the field of medical publication is very high.

G. A. H.

COLLEGE NEWS NOTES

1934 CLINICAL SESSION

The eighteenth Annual Clinical Session of the American College of Physicians will be held in Chicago, April 16-20, 1934, with headquarters at the Palmer House. As President of the College, Dr. George Morris Piersol, Philadelphia, has charge of the preparation of the program of general sessions. Dr. James B. Herrick, Chicago, was appointed General Chairman by the Board of Regents and will have charge of local arrangements. Dr. Herrick has appointed Dr. Arthur R. Elliott, Chicago, as chairman of the committee responsible for the preparation of the program of clinics in various Chicago institutions and hospitals.

APPOINTMENTS TO THE BOARD OF GOVERNORS

In accordance with provisions of the By-Laws of the American College of Physicians, Dr. George Morris Piersol, President, has made the following appointments to the Board of Governors, the appointees to hold office until the next regular election:

- Dr. Clarence L. Andrews, Atlantic City, N. J., to fill vacancy caused by the death of Dr. W. Blair Stewart;
Dr. Robert B. Kerr, Manchester, N. H., to fill vacancy caused by the death of Dr. Edward O. Otis.

Acknowledgment is made of the receipt of the following donations to the Library of the American College of Physicians by authors who are members of the College:

- Dr. Randall Clifford (Fellow), Boston, Mass.—1 book: "The Sputum: Its Examination and Clinical Significance";
Dr. William D. Reid (Fellow), Boston, Mass.—2 books: "Diseases of the Heart" and "Teaching Methods in Medicine";
Dr. Lodovico Mancusi-Ungaro (Fellow), Newark, N. J.—2 reprints;
Dr. Samuel Weiss (Fellow), New York, N. Y.—1 reprint;
Dr. Edgar F. Kiser (Fellow), Indianapolis, Ind.—1 reprint;
Dr. Hillyer Rudisill, Jr. (Fellow), Charleston, S. C.—2 reprints;
Dr. Joseph B. Wolffe (Associate), Philadelphia, Pa.—7 reprints;
Dr. Burton L. Zohman (Associate), Brooklyn, N. Y.—4 reprints.

A Committee for Survey of Research on the Gonococcus and Gonococcal Infections has been formed by the Division of Medical Sciences of the National Research Council, in coöperation with the American Social Hygiene Association. Its purpose is to collect, analyze and collate the facts already established and the efforts now in progress to add to knowledge of the gonococcus and gonococcal infections, especially as regards bacteriology, pathology, immunity, mechanism of infection and some of the forms of therapy.

Dr. Walter Clarke (Fellow), New York City, is Secretary of the Committee, and Dr. Francis Blake (Fellow), New Haven, Conn., is Chairman of the Division, ex officio.

Dr. Charles R. Drake (Fellow), Minneapolis, was recently elected by a large majority School Director of the Minneapolis Public Schools.

Dr. Marjorie E. Reed (Associate), Plymouth, Pa., recently accepted an invitation to become a member of the Editorial Board of the Child Welfare and Public Health Department of the Medical and Professional Woman's Journal.

The Extension Division of the University of Oklahoma, in coöperation with the Oklahoma State Medical Association, will offer a series of medical lectures for county medical societies in that State. Among lecturers selected to present courses, the following Fellows are included:

Dr. Lea A. Riely,
Dr. L. J. Moorman,
Dr. Ray M. Balyeat,
Dr. A. B. Chase,
Dr. John E. Heatley,
Dr. Wann Langston,
Dr. Everett S. Lain,
Dr. J. T. Martin,
Dr. E. C. Mason,
Dr. R. C. Pigford,
Dr. H. H. Turner,
Dr. A. W. White,
Dr. C. M. Pounders.

Dr. J. W. Torbett (Fellow), Marlin, Texas, addressed the American Physical Therapy Association, Chicago, September 12, 1933, on "The Recent Advances in the Dietetic Treatment of Chronic Diseases."

Dr. Isaac Seth Hirsch (Fellow) has been made Professor of Roentgenology at the New York University and Bellevue Hospital Medical College, succeeding Dr. Leon T. LeWald (Fellow), who has retired.

Dr. John I. Marker (Fellow), Davenport, Iowa, was recently elected Secretary of the Iowa and Illinois Central District Medical Association.

Dr. George S. Johnson (Associate), formerly Assistant Director of the Colorado Psychopathic Hospital of the University of Colorado, became Professor of Neuropsychiatry at Stanford University School of Medicine September 1, 1933.

Lt. Col. Harley J. Hallett (Fellow), U. S. Army, has been relieved at Fort Humphreys, Va., and assigned to the Hawaiian Department.

Major John G. Knauer (Associate), U. S. Army, has been relieved at Walter Reed General Hospital, Washington, and assigned to Balboa Heights, C. Z.

Dr. Frank N. Gordon (Fellow) has been transferred from the U. S. Veterans' Administration Hospital at Dwight, Ill., to the U. S. Veterans' Administration Hospital at Dayton, Ohio.

Dr. Bryan M. Riley (Fellow), Omaha, a member of the faculty of the Creighton University School of Medicine for the past thirty-three years, was recently appointed Dean, to succeed the late Dr. Herman von W. Schulte.

Dr. Adolph Sachs (Fellow), Omaha, also a member of the faculty for many years, succeeds Dr. Riley as Head of the Department of Internal Medicine at Creighton University and St. Joseph Hospital.

Dr. H. A. Pattison (Fellow), Livingston, N. Y., has been appointed by the National Tuberculosis Association as representative on the special After-Care Committee of the International Union Against Tuberculosis.

Dr. Joel J. White (Fellow), Lieut.-Commander, Medical Corps, U. S. Navy, who has been on duty during the past four years in Washington, D. C., as a member of the Faculty of the U. S. Naval Medical School and in charge of the Division of Aviation Medicine, Bureau of Medicine and Surgery, and also as instructor in Aviation Medicine on the Faculty of Georgetown University, School of Medicine, 1932-33 Session, has been detailed to the Staff of Admiral A. W. Johnson, Commander Aircraft, Base Force, U. S. Fleet, on the U. S. S. Wright, Flagship, based at San Diego, California.

Dr. White recently received a Letter of Commendation from the Secretary of the Navy for the development of an instrument for the analysis of the air in the cockpits and cabins of airplanes to determine carbon monoxide concentration. Dr. White is the author of an article entitled "Carbon Monoxide and Its Relation to Aircraft," which appeared in the April 1932 issue of the *Naval Medical Bulletin*.

Dr. Howard S. Brasted (Fellow), Hornell, N. Y., was recently elected Secretary of the Seventh District Branch of the New York State Medical Society.

Dr. Ralph Pemberton (Fellow), Philadelphia, Pa., Associate Professor of Medicine in the University of Pennsylvania Graduate School of Medicine and Chairman of the American Committee for the Control of Rheumatism, was the guest speaker on the occasion of a Joint Meeting of the Fifth Councilor District of the Illinois State Medical Society and the Sangamon County Medical Society, at Springfield, Ill., on October 5.

Dr. Louis Faugeres Bishop, Jr. (Fellow), New York, N. Y., has been appointed Consulting Cardiologist to The John T. Mather Memorial Hospital of Port Jefferson, New York.

Dr. J. O. Elrod (Fellow), Forsyth, Ga., was recently reappointed to the State Board of Medical Examiners for a term of four years, ending September 1, 1937.

Dr. Hillyer Rudisill, Jr. (Fellow), Charleston, S. C., is pursuing postgraduate study at the National Radium Institute, London.

Dr. Thomas A. Groover (Fellow), Washington, D. C., Chairman, Dr. Cary T. Grayson (Associate), Washington, D. C., Vice-Chairman, and Dr. William Gerry

Morgan (Fellow), Washington, D. C., Committeeman, were a Committee for the Southern Medical Association's post-meeting visit to Washington, November 18.

Dr. E. S. Lain (Fellow), Oklahoma City, Okla., received a Class I award for research on "Electro-Galvanic Lesions of the Oral Cavity Produced by Artificial Dentures" from the American Medical Association.

The Association of Life Insurance Medical Directors of America met at Toronto on October 12. Dr. Samuel B. Scholz, Jr. (Associate), Philadelphia, Pa., will act as Editor of the Proceedings. The meeting was addressed, among others, by Dr. Charles F. Martin (Master), Montreal, P. Q., Dr. Lewellys F. Barker (Fellow), Baltimore, Md., Dr. Jabez H. Elliott (Fellow), Toronto, Ont., and Dr. I. M. Rabinowitch (Fellow), Montreal, P. Q.